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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
To update the 2002 American Society of Clinical Oncology guideline on pharmacologic interventions for breast cancer (BC) risk reduction.

Methods
A literature search identified relevant randomized trials published since 2002. Primary outcome of interest was BC incidence (invasive and noninvasive). Secondary outcomes included BC mortality, adverse events, and net health benefits. An expert panel reviewed the literature and developed updated consensus guidelines.

Results
Seventeen articles met inclusion criteria. In premenopausal women, tamoxifen for 5 years reduces the risk of BC for at least 10 years, particularly estrogen receptor (ER) –positive invasive tumors. Women ≤ 50 years of age experience fewer serious side effects. Vascular and vasomotor events do not persist post-treatment across all ages. In postmenopausal women, raloxifene and tamoxifen reduce the risk of ER-positive invasive BC with equal efficacy. Raloxifene is associated with a lower risk of thromboembolic disease, benign uterine conditions, and cataracts than tamoxifen in postmenopausal women. No evidence exists establishing whether a reduction in BC risk from either agent translates into reduced BC mortality.

Recommendations
In women at increased risk for BC, tamoxifen (20 mg/d for 5 years) may be offered to reduce the risk of invasive ER-positive BC, with benefits for at least 10 years. In postmenopausal women, raloxifene (60 mg/d for 5 years) may also be considered. Use of aromatase inhibitors, fenretinide, or other selective estrogen receptor modulators to lower BC risk is not recommended outside of a clinical trial. Discussion of risks and benefits of preventive agents by health providers is critical to patient decision making.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published a technology assessment for the use of chemoprevention agents for breast cancer risk reduction in 1999.[1] ASCO guidelines are updated periodically by a subset of the original expert panel, and in 2002 the first update to the breast cancer risk reduction technology assessment was published.[2] An Update Committee met in November 2007 to review the literature published since the 2002 update and, where necessary, to update and revise the previous recommendations. Table 1 presents a summary of the updated recommendations.

ASCO's practice guidelines and technology assessments reflect expert consensus based on the best available evidence. They are intended to assist physicians and patients in clinical decision making and to identify questions and settings for further research. With the rapid flow of scientific information in oncology, new evidence can emerge between the time an updated guideline or assessment was submitted for publication and when it is read or appears in print. Guidelines and assessments are not continually updated and may not reflect the most recent evidence. Guidelines and assessments cannot account for individual variation among patients and cannot be considered inclusive of all

Table 1. Summary of Recommendations

Agent	2009 Recommendation	Dosage
Tamoxifen	May be offered to reduce the risk of ER-positive invasive BC for premenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown.	20 mg/d for 5 years
	May be offered to reduce the risk of ER-positive invasive BC for postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool), or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown.	
	Is not recommended for women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.	
	Combined use of tamoxifen for BC prevention and hormone therapy is currently not recommended.	
	Follow-up should include a baseline gynecologic examination before initiation of treatment and annually thereafter, with a timely work-up of abnormal vaginal bleeding.	
	Risks and benefits should be given careful consideration during the decision-making process.	
Raloxifene	May be offered to reduce the risk of ER-positive invasive BC in postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Impact on BC mortality is unknown.	60 mg/d for 5 years
	May be used longer than 5 years in women with osteoporosis, in whom BC risk reduction is a secondary benefit.	
	Should not be used for BC risk reduction in premenopausal women.	
	Is not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.	
	Risks and benefits should be given careful consideration during the decision-making process.	
Fenretinide	Use is not recommended outside of the clinical trial setting to lower BC risk.	NA
Aromatase inhibitors	Use is not recommended outside of the clinical trial setting to lower BC risk.	NA

Abbreviations: ER, estrogen receptor; BC, breast cancer; NCI, National Cancer Institute; LCIS, lobular carcinoma in situ; NA, not applicable.

proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment with the patient. Accordingly, adherence to any guideline or assessment is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. ASCO guidelines and assessments describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of interventions in the context of clinical trials. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO's guidelines or assessments, or for any errors or omissions.

Guideline Questions

This guideline update addresses the following clinical questions:

- In women who were not previously diagnosed with breast cancer, do tamoxifen, raloxifene, aromatase inhibitors, and/or fenretinide reduce the risk of developing breast cancer (invasive or noninvasive) compared with no pharmacologic intervention? Factors considered include disease-specific and overall mortality, type or stage of breast cancer diagnosed, and net health benefit (ie, the potential benefit of chemoprevention after taking into consideration potential harms).
- What is the comparative efficacy of tamoxifen, raloxifene, aromatase inhibitors, and fenretinide?
- What constitutes effective and responsible communication by physicians of issues regarding breast cancer risk reduction to women eligible to consider use of these agents?

Analytic Framework

The analytic framework outlined in Figure 1 describes the overall process involved in identifying women at increased breast cancer risk and informing them of available drug-based preventive options. This framework was used to guide the review of the literature, which included primary and secondary outcomes, as well as side effects from phase III randomized prevention trials, and risk communication.

UPDATE METHODOLOGY

Literature Review and Analysis

For the 2009 update, the following electronic databases were searched for articles published from January 2002 to July 2007: MEDLINE, preMEDLINE, and the Cochrane Collaboration Library. Results were supplemented with hand searching of the bibliographies of systematic reviews and selected seminal articles and contributions from Update Committee members' personal files. Search terms included the agents considered in the guideline ("tamoxifen," "raloxifene," "fenretinide," and "aromatase inhibition") as well as all of the identified brand names (North American and European). These search terms were combined with "selective estrogen receptor modulators," "breast," "mammary," "neoplasms," "cancer," "primary prevention," "preventive medicine," "prophylaxis," "risk," and "risk reduction." Searches were limited to randomized controlled trials (phase II or III), meta-analyses, systematic reviews, and existing practice guidelines. Retrospective cohort studies were permitted if they were embedded within a randomized controlled trial. Other study designs, including prospective or retrospective cohort studies

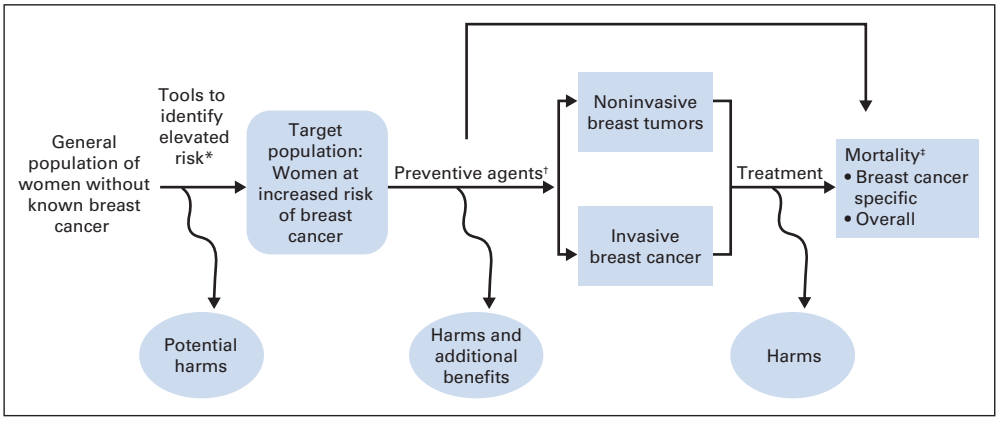

Fig 1. Analytic framework used to guide literature review. (*) Several risk predictors are available. Most incorporate age, family history, prior biopsy and histologic results, and fertility history. All models were developed in women undergoing regular breast cancer screening with mammography. (†) Tamoxifen, raloxifene, aromatase inhibitors, or fenretinide. (‡) Not the focus of this guideline because no trials have been designed with sufficient power to detect a statistically significant impact on mortality end points. Data adapted.[2a]

and phase I or phase I/II trials, were excluded. English-language studies available in full text and published in peer-reviewed journals were eligible.

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) the intervention consisted of one of the specified chemoprevention agents for the prevention of primary breast cancer; (2) participants were randomly assigned to a chemoprevention arm or a control arm (control arm could consist of no chemoprevention agent, a placebo, the same chemoprevention agent at an alternate dose/route, or a different chemoprevention agent); and (3) outcomes reported included at least one of the following: breast cancer incidence, breast cancer–specific mortality, overall mortality, net health benefits, or quality of life. The primary outcome of interest was incidence of invasive and noninvasive breast cancer (including ductal carcinoma in situ [DCIS] and lobular carcinoma in situ [LCIS]). The guideline is limited to pharmacologic interventions, and therefore evaluations of surgical and lifestyle interventions were excluded from consideration.

An initial article abstract screen was performed by two ASCO staff members who independently reviewed each abstract for inclusion criteria. Disagreements were resolved by consensus. The ASCO Update Committee cochairs reviewed the title lists of included and excluded abstracts, and full text articles were obtained for each included abstract. Full text review was undertaken by two ASCO staff, who independently reviewed each article for the inclusion criteria. Again, disagreements were resolved by consensus. Each article that met the inclusion criteria underwent data extraction for patient characteristics, study design and quality, interventions, outcomes, and adverse events. Evidence summary tables were developed based on data extracted from studies that met the criteria for inclusion. If not provided in published materials, values for absolute risk difference, number needed to treat, and number needed to harm were computed from incidence data or cumulative incidence rates provided in the published articles.

Consensus Development Based on Evidence

The Update Committee consisted of experts in clinical medicine, public health, clinical research, health services, and related disciplines (biostatistics, epidemiology, cancer prevention, patient-physician communication), with a focus on expertise in breast cancer prevention. The Update Committee also included a patient representative. A Steering Committee under the auspices of the Health Services Committee chose the Update Committee, which is listed in Appendix Table A1.

The entire Update Committee met once face-to-face. The purposes of the meeting were to review the evidence relating to each clinical question, generate the recommendations, and establish writing assignments for the respective sections. Additional work on the guideline was completed through teleconferences and electronic mail. All members of the Update Committee participated in the preparation of the draft guideline. The complete draft was reviewed and received final approval from the entire Update Committee. The guideline was submitted to *Journal of Clinical Oncology* for peer review. Feedback from external reviewers was also solicited. The content of the guidelines and the manuscript were reviewed and approved by the Health Services Committee and by the ASCO Board of Directors before publication.

Guideline and Conflicts of Interest

All members of the Update Committee complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Update Committee completed ASCO's disclosure form and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The cochairs of the Update Committee made decisions on a case-by-case basis regarding whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified. All reported conflicts of interest are listed at the end of this guideline.

RESULTS

Literature Review

Preliminary searches identified 1,329 potential articles. The abstract screen eliminated 1,241 abstracts that failed to meet any of the inclusion criteria or were duplicates resulting from searching across more than one database. Full text reports were obtained for the remaining 88 abstracts, which were reviewed in full for the interventions and outcomes described previously. Seventy-one articles were excluded at the full text review stage. Fifty-four of those were excluded

because there was no clinical end point, study design was nonrandomized, or there was no report of original data (eg, reviews of previously reported trials, editorials/commentaries). The other 17 papers were systematic reviews or meta-analyses.

Seventeen articles met the inclusion criteria for randomized controlled trials for consideration and underwent data extraction. Of these 17 articles, two reported data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene P2 (STAR) trial[3,4] comparing tamoxifen and raloxifene. Six papers reported data from the Multiple Outcomes of Raloxifene Evaluation (MORE),[5,6] Continuing Outcomes Relevant to Evista (CORE),[7,8] and/or Raloxifene Use for The Heart (RUTH)[9,10] trials, comparing raloxifene and placebo. The remaining nine articles reported data from trials comparing tamoxifen and placebo, including NSABP Breast Cancer Prevention Trial P1,[11] the International Breast Intervention Study (IBIS-I),[12-15] the Italian Randomized Tamoxifen Prevention Trial,[16-18] and the Royal Marsden Tamoxifen Prevention Trial.[19]

The literature search identified one article that combined the results from five randomized controlled trials that compared either tamoxifen or raloxifene with placebo for breast cancer prevention (NSABP-P1, Royal Marsden, Italian, IBIS-I, and MORE trials).[20] Two other meta-analyses were identified that focused on side effects of tamoxifen and summarized data from both prevention and treatment trials.[21,22]

Study Quality and Limitations of the Literature

There was heterogeneity across studies on key elements, such as participant characteristics and data reporting, which presented challenges for making comparisons between the risks and benefits of the individual agents. Additionally, meta-analyses were based on published data and not a reanalysis of original data.[20-22]

GUIDELINE RECOMMENDATIONS

TAMOXIFEN

2009 Recommendation for the Use of Tamoxifen to Reduce the Risk of Developing Breast Cancer

Five years of tamoxifen (20 mg/d) may be offered to women at increased risk of breast cancer to reduce their risk of estrogen receptor (ER) –positive invasive breast cancers for up to 10 years. Eligible women include those with a 5-year projected breast cancer risk $\geq$ 1.66% (according to the National Cancer Institute [NCI] Breast Cancer Risk Assessment Tool based on the Gail model[23] —available at http://www.cancer.gov/bcrisktool) or women with LCIS. The benefit of taking tamoxifen for more than 5 years is unknown. The greatest clinical benefit and the fewest side effects were derived from the use of tamoxifen in younger (premenopausal) women 35 to 50 years of age who are unlikely to experience thromboembolic sequelae or uterine cancer, women without a uterus, and women at high risk of breast cancer. Vascular and vasomotor side effects were observed to decline post-treatment across all ages. Tamoxifen is not recommended in women with a prior history of deep vein thrombosis (DVT), pulmonary embolus (PE), stroke, or transient ischemic attack. Combined use of tamoxifen for breast cancer prevention and hormone therapy (HT) is currently not recommended. Follow-up should include a baseline gynecologic examination before initiation of treatment and annually thereafter, with a timely work-up for abnormal vaginal bleeding. The risks and benefits of tamoxifen should be given careful consideration during the decision-making process. There has been no mortality differences observed in the tamoxifen prevention trials so far, most likely because these trials were not powered to detect such outcomes. Nevertheless, a reduction in breast cancer incidence is considered to be an important health outcome in and of itself.

Literature Update and Discussion

Clinical evidence for the use of tamoxifen for breast cancer risk reduction. Tamoxifen (Nolvadex; AstraZeneca, Wilmington, DE) is a selective estrogen-receptor modulator (SERM) and is approved by the US Food and Drug Administration (FDA) for breast cancer risk reduction in both premenopausal and postmenopausal women. Four phase III randomized trials have prospectively evaluated tamoxifen compared with placebo for breast cancer risk reduction.[20,23-26] These trials are the NSABP-P1, the IBIS-I, the Royal Marsden Tamoxifen Prevention Trial, and the Italian Randomized Tamoxifen Prevention Trial. The eligibility criteria of each trial are presented in Table 2.

On the basis of a meta-analysis of the primary results of the four tamoxifen prevention trials, the combined reduction in breast cancer incidence (invasive and DCIS) with tamoxifen use compared with placebo ranged from a relative risk (RR) of 34% (95% CI, 16% to 48%; $P = .0007$) to 38% (95% CI, 28% to 46%; $P < .0001$), depending on whether a random or fixed effects model was used.[20] There was no reduction in the risk of ER-negative breast cancer (hazard ratio [HR] = 1.22; 95% CI, 0.89 to 1.67; $P = .21$), but the incidence of ER-positive breast cancer decreased by 48% (95% CI, 36% to 58%; $P < .0001$). Age had no apparent effect on the relative degree of breast cancer risk reduction.

Follow-up data from trials evaluating tamoxifen for breast cancer risk reduction are now available and enable clinicians and patients to make informed treatment decisions based on knowledge of risks and benefits of tamoxifen use over a longer term. Tables 3, 4, and 5 present the updated results for the four tamoxifen prevention trials. Based on availability of data, for statistically significant associations, estimates of the absolute risk difference per 1,000 women, the number needed to treat (NNT) to prevent one additional outcome, and the number needed to treat to observe a particular adverse event or side effect (known as the number needed to harm [NNH]) are presented in the tables. Summary estimates or comparative estimates across the trials could not be provided as a result of significant differences in reporting of the data.

NSABP-P1 trial. The NSABP P-1 trial included 13,388 women 35 years or older who were at increased risk of breast cancer (ie, 35 to 59 years of age with a $\geq$ 1.66 risk using a modified Gail model, $\geq$ 60 years old, or with prior LCIS).[24] Women were excluded if they were using HT, oral contraceptives or androgens, or if they had used these 3 months before randomization. Participants were randomly assigned to receive placebo or tamoxifen (20 mg/d) for 5 years. The initial results were based on a median of 4.6 years (54.6 months) of follow-up. In the initial results, 89 of the 6,576 women in the tamoxifen arm developed invasive breast cancer compared with 175 of the 6,599 women in the placebo arm, which was an RR reduction of 49% (RR = 0.51; 95% CI, 0.39 to 0.66).[24] This equates to an absolute risk reduction of 15 invasive breast cancers per 1,000 women over the 4.6-year median follow-up period. There was also a 50% reduction in

Table 2. Eligibility Criteria for Tamoxifen and Raloxifene Prevention Trials

Detail/Criteria	NSABP-P1	IBIS-I	Royal Marsden	Italian	STAR	MORE	CORE (Subset of MORE)	RUTH
No. of patients randomized	6,681 (TAM) 6,707 (PLA)	3,579 (TAM) 3,575 (PLA)	1,250 (TAM) 1,244 (PLA)	2,700 (TAM) 2,708 (PLA)	9,872 (TAM) 9,875 (RAL)	5,129 (RAL) 2,576 (PLA)	2,725 (RAL) 1,286 (PLA)	5,044 (RAL) 5,057 (PLA)
Age, years	≥ 35	35-70	30-70	35-70	≥ 35	≤ 80	≤ 80	≥ 35
Entry dates	1992-1997	1992-2001	1986-1996	1992-1997	1999-2004	1994-1999	1999-2000	1998-2000
Follow-up, years	7 (mean, 6.2)	10 (median, 8.0)	20 (median, 13.2)	13 (median, 11.2)	6 (median, 4.6)	4 (median, 3.4)	4 + time in MORE trial (median, 7.9)	7 (median, 5.6)
Primary outcome	Incidence of invasive BC	Incidence of BC	Incidence of invasive BC	Incidence of BC	Incidence of invasive BC	Vertebral fractures (Incidence of BC secondary)	Incidence of invasive BC	Incidence of invasive BC and coronary events
Risk assessment	35-59 years with increased risk of BC (≥ 1.66 modified Gail* model) ≥ 60 years LCIS	35-70 years with increased risk of BC (two-fold RR for women 45-70 years of age; four-fold RR for women 40-44 years; 10-fold RR for women 35-39 years)	30-70 years with increased risk of BC (first-degree relative with BC)	35-70 years with average risk of BC Hysterectomy	≥ 35 years with increased risk of BC (≥ 1.66 modified Gail* model) Postmenopausal LCIS	≤ 80 years Postmenopausal Osteoporosis	≤ 80 years Postmenopausal Osteoporosis	≥ 55 years Postmenopausal CHD or increased risk of CHD
LCIS	Included	Included	Included	Not specified	Included	Not specified	Not specified	Not specified
AH	Included	Included	Included	Not specified	Included	Not specified	Not specified	Not specified
HT	Excluded (no concurrent HT or use of oral contraceptives or androgens within 3 months before randomization)	Included (restricted to lowest dosage necessary for symptom control)	Included (except for oral contraceptive use)	Included	Excluded (no concurrent HT or use of oral contraceptives or androgens within 3 months before randomization)	Excluded (no concurrent HT, or if on HT for more than one cycle within 6 months before trial, with the exception of occasional use of oral or topical estrogen for menopausal symptoms)		Excluded (no concurrent HT or use of oral or transdermal estrogen within 6 months before randomization)
DVT or PE (prior)	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Prior cancer	Excluded (no secondary malignancy within 10 years except nonmelanomous skin cancer and in situ cervical cancer)	Excluded	Excluded	Not specified	Excluded (except if > 5 years, or if basal or squamous cell skin cancer, or CIS of cervix)	Excluded (if estrogen-dependent malignancy, or any type of cancer within 5 years before randomization, except if superficial skin cancer)		Excluded

Abbreviations: NSABP-P1, National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial P1; IBIS-I, International Breast Intervention Study; Royal Marsden, Royal Marsden Tamoxifen Prevention Trial; Italian, Italian Randomized Tamoxifen Prevention Trial; STAR, National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene P2; MORE, Multiple Outcomes of Raloxifene Evaluation; CORE, Continuing Outcomes Relevant to Evista; RUTH, Raloxifene Use for the Heart; TAM, tamoxifen; RAL, raloxifene; PLA, placebo; BC, breast cancer; RR, relative risk; LCIS, lobular carcinoma in situ; CHD, chronic heart disease; AH, atypical hyperplasia; HT, hormone therapy; DVT, deep vein thrombosis; PE, pulmonary embolism; CIS, carcinoma in situ.
*According to the National Cancer Institute Breast Cancer Risk Assessment Tool.

noninvasive cancers in the tamoxifen arm compared with placebo (RR = 0.50; 95% CI, 0.33 to 0.77; an absolute risk reduction of six invasive breast cancers per 1,000 women over the median follow-up period). In addition, fewer ER-positive tumors were identified in the tamoxifen group (n = 41) compared with the placebo group (n = 130), with an overall RR reduction of 69% for tamoxifen users (RR = 0.31; 95% CI, 0.22 to 0.45). This equates to a reduction of 16 ER-positive breast cancers per 1,000 women over the median follow-up period. The incidence of ER-negative tumors was similar between groups, with 38 women in the tamoxifen arm compared with 31 women in the placebo group diagnosed (RR = 1.22; 95% CI, 0.74 to 2.03).

After 7 years of follow-up (including 2 years after completing therapy), the reduction in both invasive (RR = 0.57; 95% CI, 0.46 to 0.70) and noninvasive (RR = 0.63; 95% CI, 0.45 to 0.89) breast cancer persisted.[11] In absolute terms, 250 invasive breast cancers were diagnosed among the women in the placebo group compared with 145 among the women in the tamoxifen group, and there were 93 noninvasive breast cancers diagnosed in the placebo group compared with 60 in the tamoxifen group. There was no statistically significant difference in stage distribution of invasive breast cancers between the two groups. There was a reduction in ER-positive tumors of 62% in the tamoxifen group (RR = 0.38; 95% CI, 0.28 to 0.50), with 70 women in the tamoxifen group diagnosed with ER-positive tumors compared with 182 women in the placebo group. There continued to be no statistically significant difference in ER-negative tumors (RR = 1.31; 95% CI, 0.86 to 2.01). Tamoxifen consistently reduced invasive breast cancer risk, particularly ER-positive tumors, in all age strata, all 5-year predicted risk strata for breast cancer (beginning at ≥ 1.66%), and women with atypical hyperplasia (AH) or a history of LCIS. The magnitude of the protective benefit in the updated results was similar to the initial report.[24]

It is important to note that the NSABP-P1 trial unblinded participants in 1998, with subsequent differential rates of withdrawal from the placebo arm versus the treatment arm, and cross-over from the placebo arm to the tamoxifen arm. These circumstances may have biased the reported estimates of benefits and risks toward the null.

Table 3. Association Between Tamoxifen Use and BC Incidence: Results From Tamoxifen/Placebo Prevention Trials

Result	NSABP-P1				IBIS-I				Royal Marsden				Italian			
	Statistic	95% CI	AR per 1,000*	NNT*	Statistic	95% CI	AR per 1,000*	NNT*	Statistic	95% CI	AR per 1,000*	NNT*	Statistic	95% CI	AR per 1,000*	NNT*
Trial details																
Sample size included in analyses																
Tamoxifen	6,576				3,579				1,238				2,700			
Placebo	6,599				3,575				1,233				2,708			
Median follow-up period, months																
Initial	54.6[24]				50[12]				70[25]				46[26]			
Entire period	†				95.6[13,15]				158.4[19]				134.5[17]‡			
BC incidence																
BC (overall)																
Initial	NR				OR = 0.68	0.50 to 0.92	NR	NR	RR = 1.06	0.7 to 1.7			*P* = .636	NR		
Entire period					RR = 0.73	0.58 to 0.91	15	68	HR = 0.84§	0.64 to 1.10			RR = 0.84	0.60 to 1.17		
Invasive BC																
Initial	RR = 0.51	0.39 to 0.66	15	66	OR = 0.75	0.54 to 1.04			NR				NR			
Entire period					RR = 0.74	0.58 to 0.94	12	81	HR = 0.78§	0.58 to 1.04			RR = 0.80	0.56 to 1.15		
ER-positive																
Initial	RR = 0.31	0.22 to 0.45	16	63	OR = 0.69	0.47 to 1.02			NR				NR			
Entire period					RR = 0.66	0.50 to 0.87	13	80	HR = 0.61	0.43 to 0.86	26	38	RR = 0.77	0.51 to 1.16		
ER-negative																
Initial	RR = 1.22	0.74 to 2.03			OR = 1.00	0.53 to 1.87			NR				NR			
Entire period					RR = 1.00	0.61 to 1.65			HR = 1.4	0.7 to 2.6			RR = 1.10	0.59 to 2.05		
Noninvasive BC																
Initial	RR = 0.50‖	0.33 to 0.77	6	154	OR = 0.31¶	0.12 to 0.82	NR	NR	NR				NR			
Entire period					RR = 0.63¶	0.32 to 1.20			NR				RR = 1.5§	0.53 to 4.20		

Abbreviations: NSABP-P1, National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial P1; IBIS-I, International Breast Intervention Study; Royal Marsden, Royal Marsden Tamoxifen Trial; Italian, Italian Randomized Tamoxifen Prevention Trial; AR per 1,000, absolute risk difference per 1,000 women for specified median follow-up period (using published cumulative or annual incidence rates); NNT, number needed to treat to prevent one additional outcome for specified median follow-up period; BC, breast cancer; NR, not published in published literature; OR, odds ratio; RR, relative risk; HR, hazard ratio; ER, estrogen receptor.

*Computed by guideline authors using incidence data from published results. AR per 1,000 and NNT are shown only for statistically significant events.

†NSABP-P1 "Entire period" data are not reported because of potential bias resulting from unblinding of participants.

‡Mean follow-up period, months.

§Six unknown invasiveness status assumed invasive in analysis.

‖Type not specified.

¶Ductal carcinoma in situ.

Therefore, although reassuring that the reported benefits were similar 2 years after cessation of active treatment, we recommend that health providers use the estimates of benefits and risks from the original report (presented in Tables 3 and 4) in patient discussions, as these are more robust.

IBIS-I trial. IBIS-I randomly assigned 7,154 women age 35 to 70 years, who were at increased risk of breast cancer, to receive either tamoxifen (20 mg/d) or placebo for 5 years.[13] Increased risk of breast cancer was defined as a two-fold RR of breast cancer for women between the ages of 45 and 70 years, a four-fold RR for women between the ages of 40 and 44 years, or a 10-fold relative risk for women between 35 and 39 years.[28] HT was permitted but was restricted to the lowest level necessary for symptom control. The primary outcomes were the incidence of invasive and noninvasive breast cancers (including DCIS) and deaths from breast cancer. Side effects were also investigated. Interim data for the IBIS-I trial reported that tamoxifen reduced the overall risk of breast cancers by 32% (odds ratio [OR] = 0.68; 95% CI, 0.50 to 0.92) compared with placebo. Tamoxifen also reduced the incidence of invasive ER-positive tumors by 31% (OR = 0.69; 95% CI, 0.47 to 1.02). Forty-four of the 3,573 women on tamoxifen were diagnosed with invasive ER-positive tumors, as compared with 63 of 3,566 women on placebo.[12] Unlike the NSABP-P1, the majority of IBIS-I participants have remained blinded after the primary results were presented and published. The randomization code has been broken for only 10.9% of IBIS-I participants, most of whom had completed 5 years of treatment, lessening the potential for bias in the follow-up analyses.[12] Updated results, with a median follow-up of 8 years (96 months) after randomization continue to demonstrate a reduction in breast cancer risk (Tables 3, 4, and 5).[13] Table 5 presents long-term results for outcomes assessed during active treatment, post-treatment, and for the entire follow-up period. Over the entire period, there were 142 breast cancers diagnosed among the 3,579 women in the tamoxifen group and 195 among the 3,575 women in the placebo group. This equates to an absolute risk reduction of 15 breast cancers per 1,000 women over the median follow-up period. The effect of tamoxifen was constant for the entire follow-up period, and no diminution of benefit was observed for up to 10 years after randomization. The two treatment groups did not differ in the risk of ER-negative invasive tumors across the entire follow-up period (35 in each group; RR = 1.00; 95% CI, 0.61 to 1.65). However, the risk of ER-positive invasive breast cancer was 34% lower in the tamoxifen arm compared with the placebo arm (87 cases in the tamoxifen arm *v* 132 cases in the

Table 4. Association Between Tamoxifen Use and Adverse Events or Side Effects: Results From Tamoxifen/Placebo Prevention Trials

Result	NSABP-P1				IBIS-I			
	Statistic	95% CI	AR per 1,000*	NNH*	Statistic	95% CI	AR per 1,000*	NNH*
Trial details								
Sample size included in analyses								
Tamoxifen	6,576				3,579			
Placebo	6,599				3,575			
Median follow-up period, months								
Initial	54.6[24]				50[12]			
Entire period	†				95.6[13,15]			
Adverse event/side effect								
Death (any cause)								
Initial	RR = 0.81	0.56 to 1.16			*P* = .028	NR		
Entire period					RR = 1.18	0.81 to 1.73		
VTE (overall)								
Initial	NR				OR = 2.53	1.5 to 4.4		
Entire period					RR = 1.72	1.27 to 2.36	14	73
DVT								
Initial	RR = 1.60	0.91 to 2.86			*P* = .0005	NR		
Entire period					RR = 1.84‡	1.21 to 2.82	9	115
PE								
Initial	RR = 3.01	1.15 to 9.27	2	478	*P* = .68	NR		
Entire period					DVT and PE combined‡			
Cerebrovascular (overall)								
Initial	NR				*P* = .86	NR		
Entire period					RR = 0.94	0.56 to 1.57		
Stroke								
Initial	RR = 1.59	0.93 to 2.77			*P* = .84	NR		
Entire period					RR = 1.25§	0.55 to 2.93		
TIA								
Initial	RR = 0.76	0.40 to 1.44			*P* = .34	NR		
Entire period					RR = 0.77	0.39 to 1.52		
Headaches								
Initial	OR = 0.91‖	NR			*P* = .13	NR		
Entire period					RR = 0.93	0.87 to 0.99	25	39
Endometrial cancer								
Initial	RR = 2.53	1.35 to 4.97	6	158	OR = 2.20	0.80 to 6.06		
Entire period					RR = 1.55	0.68 to 3.65		
Vaginal discharge								
Initial	RR = 1.60¶[27]	NR			*P* < .0001	NR		
Entire period					NR			
Vasomotor symptoms								
Initial	RR = 1.19¶[27]	NR			*P* < .0001	NR		
Entire period					RR = 1.08#	1.06 to 1.10	64	16
Breast complaints								
Initial	OR = 0.72‖	NR			*P* < .0001	NR		
Entire period					RR = 0.77	0.70 to 0.84	58	17
Developing cataracts								
Initial	RR = 1.14	1.01 to 1.29	14	71	*P* = 1.00	NR		
Entire period					RR = 1.24	0.87 to 1.77		
Fractures								
Initial	RR = 0.81	0.63 to 1.05			*P* = .52	NR		
Entire period					RR = 1.02	0.86 to 1.21		

NOTE. Results for Royal Marsden and Italian tamoxifen prevention trials excluded due to limited data.

Abbreviations: NSABP-P1, National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial P1; IBIS-I, International Breast Intervention Study; AR per 1,000, absolute risk difference per 1,000 women for specified median follow-up period (using published cumulative or annual incidence rates); NNH, number needed to harm (the number needed to treat to observe adverse event or side effect for specified median follow-up period); RR, relative risk; NR, not reported in published literature; VTE, venous thromboembolic events; OR, odds ratio; DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

*Computed by guideline authors using incidence data from published results. AR per 1,000 and NNH are shown only for statistically significant events. Initial data unavailable for IBIS-I.

†NSABP-P1 "Entire period" data are not reported due to potential bias resulting from unblinding of participants.

‡DVT and PE combined.

§Includes cerebrovascular accident.

‖Source: Data received from personal communication with P. Ganz, November 25, 2008; values not statistically significant.

¶Placebo arm, n = 5,537; tamoxifen arm, n = 5,527.

#Vasomotor and gynecological symptoms were combined (ie, vasomotor symptoms, vaginal discharge, vaginal dryness, abnormal bleeding, endometrial polyps, uterine fibroids, amenorrhoea, thrush/*Candida*, prolapsed, ovarian cysts and lumps, endometriosis).

Table 5. Risks and Benefits Associated With Long-Term Tamoxifen Use Compared With Placebo: Results From the IBIS-I Trial[13]

Outcome	RR	95% CI	AR per 1,000*	NNT/NNH*†
BC incidence				
BC (overall)				
Active treatment	0.67	0.50 to 0.90		
Post-treatment	0.81	0.57 to 1.14		
Entire period	0.73	0.58 to 0.91	15	68
Invasive BC				
Active treatment	NR			
Post-treatment	NR			
Entire period	0.74	0.58 to 0.94	12	81
ER-positive				
Active treatment	0.74	0.51 to 1.07		
Post-treatment	0.56	0.35 to 0.87		
Entire period	0.66	0.50 to 0.87	13	80
ER-negative				
Active treatment	0.73	0.38 to 1.37		
Post-treatment	1.78	0.74 to 4.57		
Entire period	1.00	0.61 to 1.65		
Noninvasive BC (DCIS)‡				
Active treatment	NR			
Post-treatment	NR			
Entire period	0.63	0.32 to 1.20		
Adverse event/side effect				
Death (any cause)				
Active treatment	NR			
Post-treatment	NR			
Entire period	1.18	0.81 to 1.73		
VTE (overall)				
Active treatment	2.03	1.38 to 3.01		
Post-treatment	1.23	0.71 to 2.15		
Entire period	1.72	1.27 to 2.36	14	73
DVT and PE (combined)				
Active treatment	2.26	1.36 to 3.87		
Post-treatment	1.14	0.52 to 2.53		
Entire period	1.84	1.21 to 2.82	9	115
Cerebrovascular (overall)				
Active treatment	0.71	0.31 to 1.57		
Post-treatment	1.18	0.59 to 2.39		
Entire period	0.94	0.56 to 1.57		
Stroke/CVA				
Active treatment	1.00	0.33 to 3.06		
Post-treatment	1.75	0.45 to 8.16		
Entire period	1.25	0.55 to 2.93		
TIA				
Active treatment	0.44	0.10 to 1.59		
Post-treatment	1.00	0.43 to 2.34		
Entire period	0.77	0.39 to 1.52		
Headaches				
Active treatment	0.85	0.79 to 0.92		
Post-treatment	1.14	0.99 to 1.31		
Entire period	0.93	0.87 to 0.99	25	39
Endometrial cancer				
Active treatment	($P = .02$)	NR		
Post-treatment	NR			
Entire period	1.55	0.68 to 3.65		
Gynecologic/vasomotor symptoms§				
Active treatment	1.20	1.16 to 1.25		
Post-treatment	1.06	0.99 to 1.12		
Entire period	1.08	1.06 to 1.10	64	16

(continued on following page)

Table 5. Risks and Benefits Associated With Long-Term Tamoxifen Use Compared With Placebo: Results From the IBIS-I Trial[13] (continued)

Outcome	RR	95% CI	AR per 1,000*	NNT/NNH*†
Breast complaints				
Active treatment	0.73	0.67 to 0.81		
Post-treatment	0.83	0.75 to 0.92		
Entire period	0.77	0.70 to 0.84	58	17
Developing cataracts				
Active treatment	0.85	0.52 to 1.40		
Post-treatment	1.92	1.12 to 3.29		
Entire period	1.24	0.87 to 1.77		
Fractures				
Active treatment	0.85	0.67 to 1.08		
Post-treatment	1.29	0.99 to 1.69		
Entire period	1.02	0.86 to 1.21		

NOTE. Median follow-up period is 95.6 months; sample size is 3,579 for tamoxifen and 3,575 for placebo.

Abbreviations: IBIS-I, International Breast Intervention Study; RR, relative risk; AR per 1,000, absolute risk difference per 1,000 women for specified median follow-up period (using published cumulative or annual incidence rates); NNT, number needed to treat to prevent one additional outcome over specified median follow-up period; NNH, number needed to harm (the number needed to treat to observe adverse event or side effect for specified median follow-up period); BC, breast cancer; NR, not reported in published literature; ER, estrogen receptor; DCIS, ductal carcinoma in situ; VTE, venous thromboembolic events; DVT, deep vein thrombosis; PE, pulmonary embolism; CVA, cardiovascular accident; TIA, transient ischemic attack.

*Computed by guideline authors using incidence data from published results. AR per 1,000 and NNT/NNH are shown only for statistically significant events over entire follow-up period.

†NNT for breast cancer incidence; NNH for adverse event/side effect.

‡Ductal carcinoma in situ reported only.

§Vasomotor and gynecologic symptoms were combined (ie, vasomotor symptoms, vaginal discharge, vaginal dryness, abnormal bleeding, endometrial polyps, uterine fibroids, amenorrhoea, thrush/*Candida*, prolapsed, ovarian cysts and lumps, endometriosis).

placebo arm; RR = 0.66; 95% CI, 0.50 to 0.87; an absolute risk reduction of 13 ER-positive breast cancers per 1,000 women over the median follow-up period). A decrease in DCIS was also observed over 10 years of tamoxifen use, but it was not statistically significant (17 women on tamoxifen with DCIS compared with 27 women on placebo; RR = 0.63; 95% CI, 0.32 to 1.20). These follow-up results suggest that the risk-reducing effect of tamoxifen persists for at least 10 years.

Royal Marsden Tamoxifen Prevention Trial. The Royal Marsden Tamoxifen Prevention Trial randomly assigned 2,494 healthy women age 30 to 70 years to receive tamoxifen (20 mg/d) or placebo for 8 years.[19] Eligible women had an increased risk of breast cancer because of a strong family history of breast cancer. Women on HT were not excluded from the trial. Both participants and clinicians in this study remained blinded to treatment allocation during the follow-up period. Initial results showed no effect of tamoxifen on the incidence of breast cancer.[25] Further follow-up data, with a median of 13.2 years of follow-up and a maximum of 20 years, also showed no statistically significant effect of tamoxifen on the overall incidence of breast cancer (HR = 0.84; 95% CI, 0.64 to 1.10).[19] There was also no statistically significant difference in the incidence of invasive breast cancer (82 of the 1,238 women on tamoxifen and 104 of the 1,233 women on placebo had developed invasive breast cancer; HR = 0.78; 95% CI, 0.58 to 1.04). However, the incidence of ER-positive invasive breast cancer was 39% lower in the tamoxifen group over the entire period, with 53 women diagnosed, compared with 86 women diagnosed in the placebo group (HR = 0.61; 95% CI, 0.43 to 0.86; $P = .005$; an absolute reduction of 26 ER-positive breast cancers per 1,000 women over the 13.2 years median follow-up period). There was no effect of tamoxifen on the incidence of ER-positive breast cancer during active treatment (HR = 0.77; 95% CI, 0.48 to 1.23), but there was a statistically significant effect post-treatment (HR = 0.48; 95% CI, 0.29 to 0.79). The variable benefit of tamoxifen in reducing the incidence of ER-positive breast cancer during and after treatment in this study is likely a reflection of a small sample size rather than a meaningful difference when compared with the benefits observed in the NSABP-P1 and IBIS-I studies.

Italian Randomized Tamoxifen Prevention Trial. The Italian Randomized Tamoxifen Prevention Trial randomly assigned 5,408 women age 35 to 70 years with a prior hysterectomy and no prespecified breast cancer risk to receive tamoxifen (20 mg/d) or placebo for 5 years.[17] Their breast cancer risk was lower than that of the general population, because 48% of participants had undergone a bilateral oophorectomy. Women on HT were also included in the trial. Initial findings showed no effect of tamoxifen on the incidence of breast cancer.[26] The findings after an average of 11.2 years (134.5 months) of follow-up were similar, with no statistically significant reduction in overall breast cancer risk observed in the tamoxifen group (RR = 0.84; 95% CI, 0.60 to 1.17; $P = .30$). There were 62 of 2,700 women in the tamoxifen group diagnosed with breast cancer compared with 74 of 2,708 women in the placebo group.[17] However, a statistically significant reduction in progesterone receptor–positive tumors was observed among women who were taking tamoxifen compared with placebo (27 in the tamoxifen arm *v* 44 in the placebo arm; RR = 0.61; 95% CI, 0.38 to 0.99). In subgroup analyses, a reduction in breast cancer risk was observed among women at high risk with at least one ovary intact both during active treatment (HR = 0.18; 95% CI, 0.04 to 0.85) and post-treatment (HR = 0.20; 95% CI, 0.06 to 0.69). There was no effect of tamoxifen on ER-negative breast cancer (RR = 1.10; 95% CI, 0.59 to 2.05). Reporting of adverse events in this trial was limited to the period of active treatment as a result of limited follow-up.

Adverse Events and Side Effects Related to Tamoxifen Use

Since the last guideline update, three meta-analyses and follow-up data of individual risk reduction trials have provided additional information on adverse events and side effects associated with tamoxifen use. Cuzick et al[20] conducted a meta-analysis of the tamoxifen trials to examine both risks and benefits. Braithwaite et al[21] conducted a meta-analysis of vascular and neoplastic events associated with tamoxifen use in 32 randomized controlled trials, which included the four tamoxifen risk reduction trials. In this meta-analysis, subanalyses were performed on the risk reduction trials alone. Bushnell and Goldstein[22] conducted a meta-analysis on nine randomized trials, including the four tamoxifen risk reduction trials, to examine the association between ischemic strokes and tamoxifen use. Tables 4 through 8 in this guideline report the results of adverse events and side effects related to tamoxifen use from the tamoxifen and raloxifene prevention trials. Based on availability of published data, the absolute risk difference, NNT, and NNH have been included in the tables for statistically significant associations.

Endometrial cancer. The Cuzick et al[20] meta-analysis reported a more than doubling of the rate of uterine cancer with tamoxifen use (RR = 2.4; 95% CI, 1.5 to 4.0; $P = .0005$). Risks of a similar magnitude were also reported by Braithwaite et al.[21] In all of the trials, the majority of uterine cancers were stage I adenocarcinomas and were successfully treated. Endometrioid, mucinous, clear-cell, and uterine sarcoma were also reported. In the NSABP-P1 trial, an elevated risk of endometrial cancer among tamoxifen users, compared with placebo, was observed only in women 50 years of age or older. A similar trend was observed in the IBIS-I trial. In the two trials that have longer term follow-up (IBIS-I and Royal Marsden), the risk of endometrial cancer was limited to during active treatment.[13] These findings are in contrast to reports from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, in which postmenopausal women with early-stage breast cancer received adjuvant tamoxifen for 5 years compared with anastrozole, an aromatase inhibitor.[31] The current recommendation in the United States for women receiving tamoxifen includes a baseline gynecologic examination before starting tamoxifen and annual follow-up thereafter, continuing post-treatment, with a timely, thorough work-up for abnormal vaginal bleeding. Routine endometrial biopsy is not needed in the absence of abnormal vaginal bleeding. Those women with abnormalities on endometrial biopsy performed because of abnormal vaginal bleeding may consider stopping tamoxifen in consultation with their gynecologist or primary care physician.

Thromboembolic events. An increase of venous thromboembolic events (VTEs) was observed with tamoxifen use compared with placebo across all age groups in the tamoxifen prevention trials, with the exception of the Royal Marsden trial, which was conducted in a younger group of women. In their meta-analysis, Cuzick et al[20] reported a 1.9-fold (95% CI, 1.4- to 2.6-fold; $P < .0001$) increase in risk of VTEs with tamoxifen use. PE was the most frequent event, followed by DVT and retinal vein thrombosis. Tamoxifen use was associated with an even greater risk (three-fold) of superficial thrombophlebitis.[13,17] In the NSABP-P1 trial, VTEs in the tamoxifen arm were more frequent in the first 3 years.[32] In the IBIS-I trial, the risk of a VTE was not observed after cessation of treatment,[13] and factors such as surgery and/or immobilization or fracture within 1 month of starting tamoxifen were associated with a statistically significant greater risk of developing a VTE (OR = 4.7; 95% CI, 2.2 to 10.1).[14] The relative risk of developing a DVT or PE among tamoxifen users compared with placebo was 1.72 (95% CI, 1.27 to 2.36) for the entire period, which equates to an absolute risk of 14 additional cases of DVT or PE per 1,000 women among the tamoxifen group compared with the placebo group.

In the Italian trial, there was a statistically significant association between incidence of VTE and age $\geq$ 60 years, height $\geq$ 165 cm, and diastolic blood pressure $\geq$ 90 mmHg.[16] No association was observed between prothrombotic factors, such as inherited mutations of Factor V Leiden and prothrombin.[14,32] Tamoxifen is not recommended in women with a prior history of DVT, PE, stroke, or transient ischemic attack.

Stroke. Tamoxifen use for breast cancer risk reduction may result in an increase in the risk of ischemic stroke, particularly in women age 50 years or older. An increase in ischemic stroke was observed in all of the risk reduction trials, with the exception of the Royal Marsden trial, which involved a younger group of women. In a meta-analysis involving nine randomized trials (four risk reduction trials and five treatment trials), seven of which reported on stroke, women who used tamoxifen in either setting were at a greater risk of ischemic strokes (OR = 1.82; 95% CI, 1.41 to 2.36).[22] Tamoxifen is contraindicated in women with a prior history of stroke or transient ischemic attack.

Cataracts. A statistically significant increase in the incidence of cataracts (RR = 1.14; 95% CI, 1.01 to 1.29) and cataract surgery (RR = 1.57; 95% CI, 1.16 to 2.14) was observed among tamoxifen users in the NSABP-P1 trial.[24] The absolute increase in risk was 14 for newly diagnosed cataract cases per 1,000 women in the tamoxifen group compared with placebo over the median follow-up period. Women in the Royal Marsden trial who were in the tamoxifen group also experienced more cataracts during active treatment compared with women in the placebo group ($P = .02$).[19] In the IBIS-I trial, there was a statistically significant increase in cataracts observed in tamoxifen users, but only post-treatment (RR = 1.92; 95% CI, 1.12 to 3.29).[13] Tamoxifen may increase the incidence of cataracts, particularly in older women.

Cognition. Information regarding the influence of tamoxifen on cognition comes from reports of NSABP adjuvant trials B-14 and B-20, using methodology with only moderate sensitivity. The trials specifically evaluating tamoxifen and cognition suggests some negative effects, but they cannot adequately control for potential confounding factors.[33-35] Therefore, the reported effects of tamoxifen on cognition are inconclusive at this stage.

Gynecologic and vasomotor symptoms. Vaginal discharge was reported in almost 55% of women on tamoxifen in the NSABP-P1 trial (v 34% in controls), and 78% of women on tamoxifen (v 65% in controls) reported bothersome hot flashes during treatment.[27] Results from the Italian trial, which included only women who had a hysterectomy, also showed a statistically significant increase in vaginal discharge for women taking tamoxifen (RR = 3.44; 95% CI, 2.90 to 4.09).[17] Follow-up data from the IBIS-I and Royal Marsden trials suggest that these gynecologic and vasomotor symptoms are greatest during active treatment and are not increased post-treatment.[13,19] Women should be made aware that vaginal discharge and other gynecologic symptoms may be an issue with tamoxifen use.

Fractures. A potential benefit of tamoxifen is a reduction in fractures, particularly in postmenopausal women. In the NSABP-P1

Table 6. Association Between Raloxifene Use and Adverse Events or Side Effects: Results From Raloxifene/Placebo Prevention Trials

Result	CORE (Subset of MORE)				MORE				RUTH			
	Statistic	95% CI	AR per 1,000*	NNH*	Statistic	95% CI	AR per 1,000*	NNH*	Statistic	95% CI	AR per 1,000*	NNH*
Trial details												
Sample size included in analyses												
Raloxifene	2,725				5,129				5,044			
Placebo	1,286				2,576				5,057			
Median follow-up period, months												
Initial	48 (treatment)[7]				—				—			
Entire period	96 (MORE and CORE)[7]				40[5,6,29]				67.2[9]			
Adverse event/side effect												
Death (any cause)												
Initial	$P = .27$	NR										
Entire period	NR				HR = 0.61	0.36 to 1.03			HR = 0.92	0.82 to 1.03		
VTE (overall)												
Initial	RR = 2.17	0.83 to 5.70										
Entire period	$P = .094$	NR			NR				HR = 1.44	1.06 to 1.95	7	150
DVT												
Initial	$P = .49$	NR										
Entire period	$P = .32$	NR			$P = .002$	NR	NR	NR	HR = 1.37	0.94 to 1.99		
PE												
Initial	$P = .07$	NR										
Entire period	$P = .05$	NR	NR	NR	HR = 3.97†	0.91 to 17.3			HR = 1.49	0.89 to 2.49		
Cerebrovascular (overall)												
Initial	NR											
Entire period	NR				RR = 0.93†	0.64 to 1.36			NR			
Stroke												
Initial	NR											
Entire period	NR				HR = 0.68†	0.43 to 1.07			HR = 1.10	0.92 to 1.32		
TIA												
Initial	NR											
Entire period	NR				NR				NR			
Headaches												
Initial	NR											
Entire period	NR				NR				NR			
Endometrial cancer												
Initial	$P = .69$	NR										
Entire period	$P = .75$	NR			HR = 0.69†	0.22 to 2.18			$P = .53$	NR		
Gynecologic symptoms												
Initial	$P > .99$‡	NR										
Entire period	$P = .87$‡	NR			$P = .99$‡	NR			$P = .74$§	NR		
Vasomotor symptoms												
Initial	$P = .61$	NR										
Entire period	$P < .001$	NR	NR	NR	$P < .001$	NR	NR	NR	$P < .001$	NR	NR	NR
Breast complaints												
Initial	NR											
Entire period	NR				$P = .94$	NR						
Developing cataracts												
Initial	NR											
Entire period	NR				NR				$P = .56$	NR		
Fractures												
Initial	NR											
Entire period	$P < .05$‖[30]	NR	NR	NR	RR = 0.66	0.55 to 0.81	NR	NR	HR = 0.65¶	0.47 to 0.89	7	138

Abbreviations: CORE, Continuing Outcomes Relevant to Evista; MORE, Multiple Outcomes of Raloxifene Evaluation; RUTH, Raloxifene Use for the Heart; AR per 1,000, absolute risk difference per 1,000 women for specified median follow-up period (using published cumulative or annual incidence rates); NNH, number needed to harm (the number needed to treat to observe adverse event or side effect for specified median follow-up period); NR, not reported in published literature; HR, hazard ratio; VTE, venous thromboembolic events; RR, relative risk; DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

*Computed by guideline authors using incidence data from published results. AR per 1,000 and NNH are shown only for statistically significant events.

†Published data pooled doses of raloxifene (60 mg/d and 120 mg/d) for analyses.

‡Vaginal bleeding. Includes only women with intact uterus at baseline of MORE trial.

§Includes benign gynecologic growths, hyperplasia, bleeding, and "other conditions."

‖Vertebral fractures; assessed at 36 months.

¶Vertebral fractures; nonvertebral fractures HR = 0.96; 95% CI, 0.84 to 1.10.

Table 7. Comparative Efficacy of Raloxifene to Tamoxifen in STAR Trial[4]

Outcome	Raloxifene		Tamoxifen		Relative Risk	95% CI	AR† per 1,000
	No.	Rate per 1,000*	No.	Rate per 1,000*			
BC incidence							
Invasive	168	4.41	163	4.30	1.02	0.82 to 1.28	
ER-positive	109	2.86	115	3.04	0.94	0.72 to 1.24	
ER-negative	51	1.34	44	1.16	1.15	0.75 to 1.77	
Noninvasive	80	2.11	57	1.51	1.40	0.98 to 2.00	
DCIS	44	1.16	30	0.79	1.46	0.90 to 2.41	
LCIS	29	0.76	21	0.56	1.37	0.76 to 2.54	
Adverse event/side effect							
Death (all causes)	96	2.49	101	2.64	0.94	0.71 to 1.26	
Endometrial cancer	23	1.25	36	2.00	0.62	0.35 to 1.08	
Ischemic heart disease (all)	126	3.29	114	2.99	1.10	0.85 to 1.43	
Myocardial infarction	37	0.96	48	1.26	0.77	0.48 to 1.20	
Severe angina	63	1.64	51	1.34	1.23	0.84 to 1.81	
Acute ischemic syndrome	26	0.68	15	0.39	1.72	0.88 to 3.50	
Stroke	51	1.33	53	1.39	0.96	0.64 to 1.43	
Transient ischemic attack	50	1.30	41	1.08	1.21	0.79 to 1.88	
Thromboembolic event (all)	100	2.61	141	3.71	0.70	0.54 to 0.91	5
Deep vein thrombosis	65	1.69	87	2.29	0.74	0.53 to 1.03	
Pulmonary embolism	35	0.91	54	1.41	0.64	0.41 to 1.00	
Fracture	96	2.51	104	2.73	0.92	0.69 to 1.22	
Developing cataracts	313	9.72	394	12.30	0.79	0.68 to 0.92	12

NOTE. Median follow-up period is 4.6 years; sample size is 9,745 for raloxifene and 9,726 for tamoxifen.
Abbreviations: STAR, National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene P2; AR per 1,000, absolute risk difference per 1,000 women for specified median follow-up period (using published cumulative or annual incidence rates); BC, breast cancer; ER, estrogen receptor; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.
*Average annual rate per 1,000 women.
†Computed by guideline authors using incidence data from published results. AR per 1,000 shown only for statistically significant events.

trial, fractures were reported in 80 of 6,597 women in the tamoxifen group compared with 116 of 6,610 women in the placebo group, with an overall 32% relative risk reduction in hip, spine, and radius fractures observed among women who received tamoxifen compared with women on placebo (RR = 0.68; 95% CI, 0.51 to 0.92).[11] The vast majority (90%) of those fractures occurred in women age 50 years or older. However, a similar reduction in fractures was not observed in the IBIS-I trial or the Royal Marsden trial, which included, on average, a younger group of women.[13,19]

A decrease in bone mineral density of the lumbar spine was observed among participants in the Royal Marsden trial who remained premenopausal while on tamoxifen within the first year and a significant but less marked decrease in bone mineral density of the hip in the second and third year, compared with placebo.[36]

Mortality. In the Cuzick et al[20] meta-analysis, there was no overall effect of tamoxifen on all-cause mortality (HR = 0.90; 95% CI, 0.70 to 1.17; $P = .44$). PE was the only cause of death showing an increase with tamoxifen use (six events in the tamoxifen groups *v* two in the placebo groups). There were too few breast cancer deaths to comment on the effect of tamoxifen on breast cancer–specific mortality. So far, none of the prevention trials have demonstrated an effect of tamoxifen on breast cancer–specific mortality.[11,13,17,19]

Tamoxifen Use With HT

Use of menopausal HT concurrently with tamoxifen was allowed in some of the prevention trials.[13,17,19] In the IBIS-I trial, 40% of women reported using HT at some point during the trial.[13] For those women, tamoxifen was not associated with a reduction in breast cancer incidence (66 of 1,462 women on tamoxifen diagnosed with breast cancer *v* 69 of the 1,414 women on placebo; RR = 0.92; 95% CI, 0.65 to 1.31) or in ER-positive tumors (40 among women on tamoxifen *v* 43 among women on placebo; RR = 0.89; 95% CI, 0.57 to 1.41). Results were similar regardless of the HT preparations used (ie, estrogen only or combined estrogen and progestin). However, in the Royal Marsden trial, women on both tamoxifen and HT were less likely to develop ER-positive tumors (3.6 per 1,000 women on tamoxifen had ER-positive tumors per year *v* 7.9 per 1,000 in the placebo group; HR = 0.46; 95% CI, 0.23 to 0.91).[19] In the Italian trial, breast cancer risk was significantly reduced among women who were on tamoxifen and HT concurrently compared with HT and placebo, and there was no excess cardiovascular risk.[17]

The women taking HT in the Italian trial were presumably all on estrogen-only preparations because they had to have had a hysterectomy to participate in the study, as opposed to the other prevention trials. Results of the ongoing Hormone Replacement Therapy Opposed by Low Dose Tamoxifen (HOT) trial, comparing breast cancer risk in women taking HT and low-dose tamoxifen (5 mg/d) with HT alone, will hopefully help clarify potential interactions between tamoxifen and HT. So far, there have been no serious adverse effects in this trial.[37] Given the conflicting findings across trials, combined use of tamoxifen for breast cancer prevention and HT is currently not recommended.

Table 8. Comparative Efficacy of Raloxifene to Tamoxifen in the STAR* Trial: Quality-of-Life Outcomes[3]

Quality-of-Life Outcome	Difference in Average Scale Scores Over 60 Months (*P*)	Effect Size
SF-36 mental component summary†	.23	NR
SF-36 physical component summary†	.21	NR
Depression (CES-D)†	.61	NR
Sexual activity†	.04	NR
Dyspareunia‡	< .001	0.1
Vasomotor§	< .001	0.2
Weight gain‡	< .001	0.1
Musculoskeletal‡	.002	< 0.1
Bladder§	< .001	0.2
Leg cramps§	< .001	0.2
Gynecologic§	< .001	0.3

Abbreviations: STAR, National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene P2; SF-36, Medical Outcomes Study Short Form 36; NR, not reported; CES-D, Center for Epidemiologic Studies–Depression Scale.

*Median follow-up, 5.4 years.

†These data were collected on a subsample from the STAR trial (1,010 women on raloxifene and 973 women on tamoxifen).

‡Favors tamoxifen.

§Favors raloxifene.

Duration of Tamoxifen Treatment for Risk Reduction

The use of tamoxifen for periods longer than 5 years is being evaluated in the adjuvant treatment setting, but conclusive data on this issue are not yet available.[38] There are limited data on tamoxifen use for more than 5 years in the setting of risk reduction, and therefore, it is recommended that the duration of tamoxifen be limited to 5 years outside of a clinical trial setting.

RALOXIFENE

2009 Recommendation for the Use of Raloxifene to Reduce the Risk of Developing Breast Cancer

For postmenopausal women at increased risk for breast cancer, raloxifene (60 mg/d) for 5 years may be offered as another option to reduce the risk of ER-positive invasive breast cancer. Raloxifene has been shown to be equally efficacious to tamoxifen in reducing breast cancer risk in postmenopausal women. However, raloxifene was not as effective in reducing the incidence of noninvasive breast cancer compared with tamoxifen, although the association was not statistically significant. In the STAR trial, raloxifene was associated with a more favorable side-effect profile compared with tamoxifen, including a statistically significant lower risk of thromboembolic disease, benign uterine complaints, and cataracts as compared with tamoxifen. Raloxifene, like tamoxifen, is not known to have an effect on overall or breast cancer–specific mortality in women at increased risk of breast cancer. However, the risk reduction trials were not powered to detect a reduction in breast cancer incidence rather than mortality, as it was felt to be an important end point in and of itself. Raloxifene may be used for longer than 5 years in women with osteoporosis in whom breast cancer risk reduction is an additional potential benefit. Raloxifene is not recommended in premenopausal women or in women with a prior history of DVT, PE, stroke, or transient ischemic attack. In postmenopausal women, the risks and benefits of both tamoxifen and raloxifene, including risks of noninvasive breast cancer, adverse events, and impact on quality of life, should be discussed in detail with women before coming to a decision about risk reduction strategies.

Literature Update and Discussion

Clinical evidence for the use of raloxifene for breast cancer risk reduction. Raloxifene (Evista; Lilly, Indianapolis, IN) is approved by the FDA for treating and preventing osteoporosis in postmenopausal women and for reducing the risk of invasive breast cancer in postmenopausal women at increased risk of breast cancer. Raloxifene does not have demonstrated activity against established breast cancer, and raloxifene should not be used to treat breast cancer or prevent its recurrence.[39] Four randomized prospective trials have evaluated the influence of raloxifene on breast cancer risk.[4,7,10,29] Risk reduction was the primary end point of two trials, the STAR and RUTH trials,[4,10] and a secondary end point of the MORE trial.[7,29] It was also the primary end point of the CORE trial, which followed a subgroup of participants from the MORE trial. Although the eligibility criteria for these trials differed, raloxifene use was consistently associated with a reduction in breast cancer risk. Table 2 presents the eligibility criteria for each of these trials, and Tables 6 and 9 present the results of each trial, including associated adverse events and side effects. The absolute risk difference, NNT, and NNH are included for statistically significant associations when published data are available.

MORE and CORE trials. The earliest information on raloxifene and breast cancer risk came from the MORE study of 7,705 postmenopausal women with osteoporosis who were ≤ 80 years of age (mean age, 66.5 years).[29] Participants were randomly assigned to receive raloxifene (60 or 120 mg/d) or placebo for 4 years. Women were excluded if they had used HT for more than one cycle within 6 months before the beginning of the trial, with the exception of occasional use of oral or topical estrogen for menopausal symptoms. HT use was not permitted during the trial. Participants were entered regardless of breast cancer risk, which was not formally assessed at study entry, although information on breast cancer family history was collected and presented. Breast cancer was a secondary outcome. The most recent MORE update focused only on women for whom information was available on prior HT use.[6] There were a total of 78 cases of breast cancer in 7,682 women who reported on whether or not they had previously taken HT (44 breast cancers in 2,571 women in the placebo group, compared with 34 of the 5,111 women in the raloxifene group [combining both dosage arms]; RR = 0.38; 95% CI, 0.24 to 0.58). Of those, 59 were invasive breast cancer and 19 were noninvasive. Women treated with raloxifene had a statistically significant reduced risk of invasive breast cancer compared with women on placebo (21 women on raloxifene developed invasive breast cancer compared with 38 women on placebo; RR = 0.28; 95% CI, 0.17 to 0.46), particularly ER-positive invasive breast cancer (RR = 0.16; 95% CI, 0.09 to 0.30).

After the completion of the MORE trial, consenting participants were observed under an amended design called the CORE trial, which reconsented 4,011 MORE trial participants (52%) and kept them on their original treatment assignments, except for

Table 9. Association Between Raloxifene Use and BC Incidence: Results From Raloxifene/Placebo Prevention Trials

Outcome	CORE (Subset of MORE)				MORE*				RUTH			
	Statistic	95% CI	AR per 1,000†	NNT†	Statistic	95% CI	AR per 1,000†	NNT†	Statistic	95% CI	AR per 1,000†	NNT†
Trial details												
Sample size included in analyses												
Raloxifene												
Initial	3,510				5,129				—			
Entire period	5,129				5,111				5,044			
Placebo												
Initial	1,703				2,576				—			
Entire period	2,576				2,571				5,057			
Median follow-up period, months												
Initial	48 (CORE trial alone)[7]				40[29]				—			
Entire period	96 (MORE and CORE combined)[7]				48 (includes only women with known HT status) [6]				67.2[9]			
BC incidence												
BC (overall)												
Initial	HR = 0.50	0.30 to 0.82	11	89	RR = 0.35	0.21 to 0.58	9	107				
Entire period	HR = 0.42	0.29 to 0.60	NR	NR	RR = 0.38	0.24 to 0.58	NR	NR	HR = 0.67	0.47 to 0.96	5	200
Invasive BC												
Initial	HR = 0.41	0.24 to 0.71	12	81	RR = 0.24	0.13 to 0.44	9	111				
Entire period	HR = 0.34	0.22 to 0.50	22	45	RR = 0.28	0.17 to 0.46	NR	NR	HR = 0.56	0.38 to 0.83	7	150
ER-positive												
Initial	HR‡ = 0.34	0.18 to 0.66	10	96	RR = 0.10	0.04 to 0.24	NR	NR				
Entire period	HR = 0.24	0.15 to 0.40	19	52	RR = 0.16	0.09 to 0.30	NR	NR	HR = 0.45	0.28 to 0.72	7	150
ER-negative												
Initial	HR = 1.13	0.29 to 4.35			RR = 0.88	0.26 to 3.00						
Entire period	HR = 1.06	0.43 to 2.59			NR				HR = 1.44	0.61 to 3.36		
Noninvasive BC												
Initial	HR = 1.78	0.37 to 8.61			NR							
Entire period	HR = 1.12	0.46 to 2.73			NR				HR = 2.17	0.75 to 6.24		

Abbreviations: BC, breast cancer; CORE, Continuing Outcomes Relevant to Evista; MORE, Multiple Outcomes of Raloxifene Evaluation; RUTH, Raloxifene Use for the Heart; AR per 1,000, absolute risk difference per 1,000 women for specified median follow-up period (using published cumulative or annual incidence rates); NNT, number needed to treat to prevent one additional outcome for specified median follow-up period; HT, hormone therapy; HR, hazard ratio; RR, relative risk; NR, not reported in published literature; ER, estrogen receptor.

*Published data pooled doses of raloxifene (60 and 120 mg/d) for analyses.

†Computed by guideline authors using incidence data from published results. AR per 1,000 and NNT are shown only for statistically significant events.

‡Among CORE enrollees, ER status was only determined on 73% of the breast cancers.

reducing those on 120 mg/d of raloxifene to 60 mg/d (the FDA-approved dose for osteoporosis).[7] Most participants had a gap in their course of study medication between completing MORE and joining the CORE trial (median gap of 10.6 months; range, 2.6 to 62 months). CORE participants had 5-year breast cancer risk assessed at study entry with the Gail model.[40] CORE data showed that 4 years of additional raloxifene use reduced invasive breast cancer by 59% compared with placebo and ER-positive invasive breast cancer by 66% compared with placebo.[7] There were 28 of 1,703 women in the placebo group diagnosed with invasive breast cancer compared with 24 of 3,510 women in the raloxifene group (HR = 0.41; 95% CI, 0.24 to 0.71; $P < .001$; an absolute reduction of 12 cases of invasive breast cancer per 1,000 women), and 21 of the women in the placebo group were diagnosed with ER-positive invasive breast cancer compared with 15 in the raloxifene group (HR = 0.34; 95% CI, 0.18 to 0.66; $P < .001$; an absolute reduction of 10 ER-positive breast cancer cases per 1,000 women). Through 8 years of randomization from the MORE trial to the end of the CORE trial, raloxifene continued to significantly reduce the risk of overall breast cancer (HR = 0.42; 95% CI, 0.29 to 0.60; $P < .001$), invasive breast cancer (HR = 0.34; 95% CI, 0.22 to 0.50), and ER-positive breast cancer (HR = 0.24; 95% CI, 0.15 to 0.40). The incidence of ER-negative invasive breast cancer was similar in the two treatment groups throughout the 8 years of treatment (HR = 1.06; 95% CI, 0.43 to 2.59; $P = .86$).

RUTH trial. The RUTH trial tested raloxifene (60 mg/d) versus placebo in 10,101 postmenopausal women with coronary heart disease or multiple risk factors for coronary heart disease.[9] The two primary outcome measures were coronary events and invasive breast cancer. Participants were entered regardless of breast cancer risk, and only 41% had a 5-year predicted breast cancer risk of $\geq$ 1.66%. Women were excluded if they were currently receiving HT or if they had used oral or transdermal estrogen within 6 months before randomization. Raloxifene use did not influence the risk of primary coronary events (HR = 0.95; 95% CI, 0.84 to 1.07).[9] However, raloxifene significantly reduced invasive breast cancer risk (40 of 5,044

women in the raloxifene group *v* 70 of 5,057 in the placebo group; HR = 0.56; 95% CI, 0.38 to 0.83), primarily due to reduced ER-positive breast cancer (25 women on raloxifene *v* 55 on placebo developed ER-positive breast cancer; HR = 0.45; 95% CI, 0.28 to 0.72). This translates to an absolute risk reduction of seven invasive breast cancers and seven ER-positive breast cancers per 1,000 women over the median follow-up period.

NSABP STAR trial. The STAR trial randomly assigned 19,747 postmenopausal women with a 5-year increased risk of breast cancer (ie, 5-year increased risk of ≥ 1.66% using the NCI Breast Cancer Risk Assessment Tool [http://www.cancer.gov/bcrisktool] based on the Gail model[23]) to tamoxifen (20 mg/d) or raloxifene (60 mg/d) for 5 years.[4] This was the same risk assessment used in NSABP-P1. Women receiving hormone therapy, or with uncontrolled diabetes mellitus, hypertension, or a past history of stroke, were excluded from the trial. The primary end point was a reduction in breast cancer risk. The mean age of participants was 58.5 years, and their baseline characteristics were substantially different from the prior NSABP-P1 tamoxifen prevention trial. In particular, their 5-year projected breast cancer risk was higher (58.7% had a > 3% 5-year projected breast cancer risk in the STAR trial, compared with 44% in the NSABP-P1 trial).[4,11] In addition, more than 51% of STAR participants had a prior hysterectomy as compared with 37% of participants in the NSABP-P1 tamoxifen prevention trial. More than 32% of STAR participants had a history of breast LCIS or AH compared with 15% of NSABP-P1 participants. These differences may reflect the concerns that women and their health care providers had about the adverse effects associated with tamoxifen use (eg, increased risk of endometrial cancer).

Table 7 presents the results from the STAR trial, comparing raloxifene and tamoxifen. The incidence of invasive breast cancer in the tamoxifen and raloxifene groups were not significantly different.[4] There were 168 of 9,745 women on raloxifene diagnosed with invasive breast cancer compared with 163 of 9,726 women on tamoxifen (4.41 per 1,000 women on raloxifene per year compared with 4.30 per 1,000 women on tamoxifen per year; RR = 1.02; 95% CI, 0.82 to 1.28). There were more noninvasive breast cancers in the raloxifene (n = 80) group than in the tamoxifen (n = 57) group (RR = 1.40; 95% CI, 0.98 to 2.00), but the difference was not statistically significant. Findings were also comparable for women diagnosed with ER-positive tumors (109 women in the raloxifene group *v* 115 women in the tamoxifen group; RR = 0.94; 95% CI, 0.72 to 1.24).

Adverse Events and Side Effects Related to Raloxifene Use

Endometrial cancer. There was no statistically significant increase in uterine cancer when raloxifene was compared with placebo in the MORE, CORE, or RUTH trials.[4,5,9] In the STAR trial, a nonsignificant decrease in uterine cancer was observed in women taking raloxifene compared with tamoxifen (RR = 0.62; 95% CI, 0.35 to 1.08), but the number of cases was small: 36 of the 9,726 women in the tamoxifen arm and 23 of the 9,745 women in the raloxifene arm.[4] Of 56 women with known stage of disease, 91% were stage I. As part of the trial, all women underwent annual gynecologic examinations. There were significantly fewer diagnoses of uterine hyperplasia with atypia in the raloxifene arm compared with the tamoxifen arm (12 women receiving tamoxifen *v* one woman receiving raloxifene; RR = 0.08; 95% CI, 0 to 0.55) and without atypia (72 women receiving tamoxifen *v* 13 women receiving raloxifene; RR = 0.18; 95% CI, 0.09 to 0.32), as well as hysterectomies performed for non–cancer-related reasons during the course of follow-up (244 women on tamoxifen *v* 111 women on raloxifene; RR = 0.44; 95% CI, 0.35 to 0.56).[4]

VTEs. VTEs were increased in the raloxifene arm compared with placebo in the CORE and CORE plus MORE analyses, but did not reach statistical significance.[7] In the RUTH trial, the likelihood of a VTE was 44% higher in the raloxifene group compared with placebo (103 of 5,044 women receiving raloxifene *v* 71 of 5,057 women receiving placebo; HR = 1.44; 95% CI, 1.06 to 1.95; *P* = .02).[9] A 30% decrease in VTEs was observed in the raloxifene group compared with the tamoxifen group in the STAR trial (141 of the 9,726 women on tamoxifen *v* 100 of the 9,745 women on raloxifene; RR = 0.70; 95% CI, 0.54 to 0.91).[4] A reduction was observed separately for PE (54 women on tamoxifen *v* 35 women on raloxifene; RR = 0.64; 95% CI, 0.41 to 1.00) and DVT (87 women on tamoxifen *v* 65 women on raloxifene; RR = 0.74; 95% CI, 0.53 to 1.03).

Ischemic heart disease. In the MORE, CORE, and RUTH trials, there were no statistically significant differences in the incidence of cardiac events between the raloxifene and placebo arms.[4,5,9] In the STAR trial, there was no significant difference in ischemic heart disease between the raloxifene and tamoxifen arms of the trial.[4]

Stroke. In the STAR, CORE, and MORE trials, there was no difference in the incidence of stroke between the raloxifene group and the tamoxifen (STAR trial) or placebo (CORE and MORE) groups.[4-7] In the STAR trial, however, women with a prior stroke or certain risk factors, such as uncontrolled diabetes, hypertension, or atrial fibrillation, were excluded. In the RUTH trial, among women with underlying coronary disease or at risk for it, the incidence of fatal strokes alone was 49% higher in the raloxifene group compared with placebo (59 of 5,044 women on raloxifene *v* 39 of 5,057 women on placebo; HR = 1.49; 95% CI, 1.00 to 2.24; *P* = .05).[9] These findings suggest that women with underlying vascular disease should not be treated with raloxifene.

Cataracts. The incidence of cataracts was not increased in women taking raloxifene compared with placebo in either the RUTH, MORE, or CORE trials.[7,9] Among those who were free of cataracts at baseline, women on the raloxifene arm in the STAR trial were less likely to develop cataracts (394 of 9,726 women on tamoxifen developed cataracts *v* 313 of 9,745 women on raloxifene; RR = 0.79; 95% CI, 0.68 to 0.92) or have cataract surgery (260 of 9,726 women on tamoxifen *v* 215 of 9,745 women on raloxifene; RR = 0.82; 95% CI, 0.68 to 0.99) than women on the tamoxifen arm.[4] This difference became evident after the first 2 years after randomization.

Cognition. The influence of raloxifene on cognitive function was assessed as part of the MORE trial[41] In 7,478 postmenopausal women, raloxifene at 60 mg/d or 120 mg/d for 3 years did not negatively influence cognitive scores. Subsequent analyses found an association between the higher 120 mg/d raloxifene dose and lower rates of cognitive impairment,[42] and similar findings were reported in another randomized trial.[43] However, raloxifene effects on cognition in smaller studies provide mixed results.[44-46] In a substudy of the STAR trial with 1,983 participants, there was no statistically significant change over time in self-reported forgetfulness in either the raloxifene or tamoxifen arms. A more detailed assessment of cognitive change associated with tamoxifen and raloxifene use may emerge from an

ancillary study (Co-STAR) being conducted in 1,510 participants recruited from the STAR trial (NCT00687102). Participants will undergo annual neuropsychological assessments of verbal and nonverbal memory and mood, with results anticipated in 2009.[3]

Gynecologic and vasomotor symptoms. Among women in the STAR trial included in an analysis of gynecologic and vasomotor symptoms, women on tamoxifen reported more gynecologic and vasomotor symptoms than women on raloxifene ($P < .001$ for both).

Fractures. Fracture rate was not statistically significantly different between arms in the STAR trial (RR = 0.92; 95% CI, 0.69 to 1.22). Although fractures were not a primary end point for the STAR trial, information was collected for hip, spine, and Colles' fractures at each follow-up visit and verified through medical documentation.[4] In the RUTH trial, there was a 35% decrease in the incidence of vertebral fractures in the raloxifene group when compared with placebo (64 of 5,044 women on raloxifene *v* 97 of 5,057 women on placebo; HR = 0.65; 95% CI, 0.47 to 0.89).[9] Therefore, both raloxifene and tamoxifen are effective in reducing fractures in postmenopausal women. Raloxifene use has been associated with a significant decrease in bone mineral density in premenopausal women.[47]

Mortality. In the STAR trial, there was no difference in the numbers and causes of death between the two arms.[4] There were 101 deaths in the 9,726 women in the tamoxifen arm compared with 96 deaths in the 9,745 women in the raloxifene arm (RR = 0.94; 95% CI, 0.71 to 1.26). Four women in the tamoxifen arm and two in the raloxifene arm died of breast cancer. There was no effect of raloxifene on the incidence of death in the MORE, CORE, or RUTH trials.[7,9] In the RUTH trial, there was a statistically significant increase in fatal strokes (HR = 1.49; 95% CI, 1.00 to 2.24).[9] It is important to note, however, that these studies were not powered to observe significant differences in mortality over their follow-up periods.

Ongoing Risk Reduction Benefit With Raloxifene

Results of the CORE trial indicate that raloxifene use for 8 years (4 years on the MORE trial followed by 4 years on the CORE trial) continued to demonstrate the reduction in ER-positive invasive breast cancer, but had no impact on ER-negative breast cancers, in postmenopausal women with osteoporosis.[7] The increased raloxifene-related risk of thromboembolism continued during the CORE trial, although it was not statistically significant (RR = 2.17; 95% CI, 0.83 to 5.70), whereas endometrial cancer and stroke incidences were similar in the raloxifene and placebo groups.

Comparing Quality of Life for Tamoxifen and Raloxifene

Tables 4, 6, and 8 present findings related to quality of life for tamoxifen and raloxifene breast cancer prevention trials. In all of the tamoxifen prevention trials that compare tamoxifen with placebo, there was a statistically significant increase in vasomotor and gynecologic symptoms.[12,17,19,24,48] There was no significant difference in weight gain or depression scores between the two arms in those studies that reported on them. The NSABP-P1 results also noted that women on tamoxifen reported a small but significant increase in problems related to sexual functioning compared with those on placebo, although the overall frequency of sexual activity was similar in the two groups.[27]

Comparative information regarding the influence of tamoxifen and raloxifene on patient-reported symptoms and quality of life is available from the STAR trial.[3] Quality of life was assessed with the Medical Outcome Study Short Form–36, which provides scales for physical functioning and mental health.[49] Depressive symptoms were measured with the Center for Epidemiologic Studies–Depression Scale.[50] Among women in the STAR trial included in the quality-of-life analyses, the mean scores of all three measures decreased modestly during the study for both arms, with no major difference observed between the two groups.

Statistically significant differences in the average mean severity of individual quality-of-life measures between the two arms were observed and are reported in Table 8. An increase in gynecologic symptoms, vasomotor symptoms, leg cramps, and bladder control problems was observed in both groups during treatment, with the difference being significantly greater for the tamoxifen group compared with the raloxifene group ($P < .001$ for all symptoms). In contrast, women in the raloxifene group reported significantly more musculoskeletal problems, dyspareunia, and weight gain ($P \leq .002$ for all symptoms). Despite being statistically significant, these differences were associated with small effect sizes. Similar findings for raloxifene were reported in the raloxifene placebo-controlled trials (ie, RUTH, CORE, and MORE trials). In the RUTH trial, hot flashes, leg cramps, and peripheral edema were significantly more common in the raloxifene arm compared with placebo ($P < .001$ for all symptoms). Hot flashes ($P < .001$) and leg cramps ($P = .008$), but not peripheral edema ($P = .24$), were also more common in the raloxifene arm compared with the placebo arm of the MORE and CORE trials. These findings illustrate that potential adverse effects on components of quality of life should be taken into consideration when discussing risk reduction options.

AROMATASE INHIBITORS

2009 Recommendation for the Use of Aromatase Inhibitors to Reduce the Risk of Developing Breast Cancer

The Update Committee does not recommend the use of any aromatase inhibitor to lower breast cancer risk outside of the investigational setting. Ongoing studies will offer more data for the next review of this area.

Literature Update and Discussion

Clinical evidence for the use of aromatase inhibitors for breast cancer risk reduction. Phase III clinical trials of aromatase inhibitors are ongoing (Table 10). The effects of aromatase inhibitors (anastrozole, letrozole) and inactivators (exemestane) on contralateral breast cancer risk support further evaluation of these agents for breast cancer risk reduction. A meta-analysis of adjuvant breast cancer trials evaluating aromatase inhibitors identified a 48% relative reduction in contralateral breast cancer risk with five of the six comparators being tamoxifen.[52] The concept of using aromatase inhibitors as a breast cancer risk reduction agent was strengthened by the recent update of the ATAC trial, in which, with 100 months of follow-up, 5 years of anastrozole was associated with fewer contralateral breast cancers as a first event compared with 5 years of tamoxifen (for hormone receptor–

Table 10. Status of Ongoing Randomized Trials for BC Chemoprevention

Study	Entry Criteria	Intervention	Target Accrual	Status
Hormone Replacement Therapy Opposed by Low-Dose Tamoxifen (HOT)[51]	Postmenopausal healthy women using HT who are at increased risk for BC	All receive HT tamoxifen 5 mg/d × 5 years *v* placebo × 5 years	8,500	Accrual started (N = 1,870 as of December, 2006[34])
International Breast Intervention Study-II (IBIS-II)[52]	Increased BC risk; age 40-70 years; postmenopausal; LCIS, AH, DCIS (treated in last 6 months by mastectomy) allowed	Anastrozole 1 mg/d × 5 years *v* placebo × 5 years	6,000	Accrual started (N = 4,178 as of December, 2008[53])
MAP.3 (ExCel)[54]	≥ 35 years of age; postmenopausal; increased risk for BC	Exemestane 25 mg/d × 5 years *v* placebo × 5 years	4,560	Accrual started (N = 3,616 as of January, 2009*)
Aromasin Prevention Study (ApreS)[55]	Postmenopausal, unaffected *BRCA1/2* mutation carriers	Exemestane 25 mg/d × 5 years *v* placebo × 5 years	666	Accrual started (status not available)

Abbreviations: BC, breast cancer; HT, hormonal therapy; LCIS, lobular carcinoma in situ; AH, atypical hyperplasia; DCIS, ductal carcinoma in situ.
*D. Johnston, personal communication, January 2009.

positive patients; HR = 0.60; 95% CI, 0.42 to 0.85; $P = .004$).[31] The International Breast Intervention Study-II (IBIS-II) is randomly assigning 6,000 postmenopausal women at increased breast cancer risk to 5 years of placebo or anastrozole (1 mg/d), whereas the ExCel Study (MAP.3) trial is randomly assigning postmenopausal women either at increased breast cancer risk or age ≥ 60 years to 5 years of exemestane (25 mg/d) or placebo, with a sample size of 4,560 participants.[54]

These full-scale clinical trials are placebo controlled and involve discussion of the two approved agents (tamoxifen, raloxifene) for breast cancer risk reduction as part of the consent process. It was the judgment of the investigational teams and the trials' regulatory agencies that the study design was appropriate for women at elevated risk of breast cancer who had chosen to not use tamoxifen or raloxifene.[31,56] A recent report of findings from the IBIS-II study found no effect of anastrozole on cognition.[57]

RETINOIDS

2009 Recommendation for the Use of Retinoids to Reduce the Risk of Developing Breast Cancer

The Update Committee does not recommend the use of retinoids, such as fenretinide, to lower breast cancer risk outside of the investigational setting.

Literature Update and Discussion

Clinical evidence for the use of retinoids for breast cancer risk reduction. To date, fenretinide is the only retinoid that has been evaluated in a phase III study for secondary breast cancer prevention.[58] Approximately 3,000 women age 30 to 70 years with a diagnosis of DCIS or stage I breast cancer were randomly assigned to receive 5 years of fenretinide (200 mg/d) or no treatment, in addition to standard therapy. Half of the women were recruited immediately after surgery, whereas the other half were recruited within 10 years of diagnosis, provided they did not have chemotherapy and were recurrence free. The primary end point of this study was the incidence of second breast cancers. At a median follow-up time of 97 months, there was no statistically significant difference in overall breast cancer incidence between the two arms. However, in a post hoc analysis, a nonsignificant reduction in breast cancer risk was observed in premenopausal women (HR = 0.66; 95% CI, 0.41 to 1.07).[59]

Further follow-up of a subset of women (59%) over a median of almost 15 years continued to observe no difference in overall breast cancer incidence between the two groups. In a subset analysis, a statistically significant reduction in second primary breast cancer was observed among the premenopausal women treated with fenretinide (HR = 0.62; 95% CI, 0.46 to 0.83) compared with no treatment, suggesting that this group may benefit from such an agent.[58] No difference was observed in overall mortality between the study arms. In this study, fenretinide was relatively well tolerated. Dermatologic and dark-vision adaptations were the most common adverse events. Fenretinide is now being studied in combination with tamoxifen for the prevention of breast cancer in high-risk women.[60]

COMPARATIVE EFFICACY AND SIDE EFFECT PROFILE OF TAMOXIFEN, RALOXIFENE, AROMATASE INHIBITORS, AND RETINOIDS FOR BREAST CANCER RISK REDUCTION

Follow-up data from the phase III prevention trials have established a net benefit of tamoxifen use for the reduction of ER-positive breast cancers, particularly in women younger than 50 years, with continued benefit for at least 10 years.[3-19] The results of the STAR trial have confirmed the risk reduction effects of raloxifene in postmenopausal women.[4] Although equally efficacious at decreasing invasive breast cancer in the short term, the effect of raloxifene on DCIS and side effects differs from that of tamoxifen. A greater reduction in DCIS was observed in the tamoxifen arm, whereas raloxifene had a better side effect profile.[4] Further, up to 8 years of raloxifene use (albeit with a gap in treatment) for osteoporosis was associated with continued breast cancer risk reduction.[5-7]

Tamoxifen and raloxifene had a similar favorable effect on fracture incidence. They both increased the incidence of venous vascular events, but the influence of tamoxifen on such events appears somewhat greater. It is likely that tamoxifen and raloxifene increase arterial vascular events to a similar degree. The effect of both agents on arterial vascular events appeared to be higher in older women and women with known risk factors for such events. Women who were treated with raloxifene had fewer uterine cancers, gynecologic symptoms, and cataracts compared with women who were treated with tamoxifen.

Overall quality of life was similar in the raloxifene and tamoxifen arms of the STAR trial, but the incidence of dyspareunia, weight gain,

and musculoskeletal complaints was higher with raloxifene use, whereas vasomotor symptoms, bladder incontinence, gynecologic symptoms, and leg cramps were higher with tamoxifen use.

All of the prevention trials used reduced breast cancer incidence, rather than reduced mortality, as the primary end point. To design a prevention trial that has the power to determine a reduction in mortality would require a much longer follow-up and expense. Therefore, it is unlikely that meaningful mortality data will be known from any of these trials because of the limited power for this end point, the long follow-up time necessary, and the effects of unblinding in certain trials. A meta-analysis of all of the risk reduction trials using tamoxifen and raloxifene is ongoing (J. Cuzick, personal communication, December 2008).

Aromatase inhibitors and retinoids both have the potential to reduce breast cancer risk. Unlike tamoxifen and raloxifene, they are not currently approved by the FDA for breast cancer risk reduction. Ongoing risk reduction trials with aromatase inhibitors and retinoids will provide more important evidence about their effects on breast cancer risk reduction and their risks.

OTHER ISSUES

ER-Negative Breast Cancer

All of the breast cancer risk reduction trials using SERMs demonstrate that these agents are effective in reducing the risk of only ER-positive breast cancer. They do not prevent the development of ER-negative breast cancer, which accounts for 30% of all breast cancers in white populations, and an even higher proportion (40% or more) in African American populations. Tamoxifen did, however, seem to increase the sensitivity of mammography for the detection of ER-negative tumors in the NSABP-P1 trial. ER-negative tumors were found earlier and were smaller in women treated with tamoxifen in comparison with women on placebo.[61] There is a need to develop agents that also prevent ER-negative breast cancer. Several classes of chemopreventive agents have been shown to prevent ER-negative breast cancer in animal models. These include retinoids and rexinoids (9-cis retinoic acid, bexarotene, and LG100268),[62-64] the Cox-2 inhibitor celecoxib,[65] and tyrosine kinase inhibitors (gefitinib and lapatinib).[66,67] Several of these agents are now being tested in early-phase risk reduction trials involving biomarker modulation. It is possible that, in the future, these cancer risk reduction drugs will be combined with hormonal agents (such as SERMs or aromatase inhibitors) to reduce the risk for both ER-positive and ER-negative breast cancer.

Risk Reduction for BRCA1 *and* BRCA2 *Mutation Carriers*

There are limited data on the efficacy of tamoxifen for breast cancer risk reduction in *BRCA1* and *BRCA2* mutation carriers. The NSABP evaluated the effect of tamoxifen on breast cancer risk in NSABP-P1 participants with inherited *BRCA1* or *BRCA2* mutations.[68] Of 288 women who developed breast cancers, only 19 women had either *BRCA1* or *BRCA2* mutations. Tamoxifen did not have a statistically significant effect on breast cancer risk in women with *BRCA2* mutations, in whom tumors were largely receptor-positive (RR = 0.38; 95% CI, 0.06 to 1.56), or in women with *BRCA1* mutations (RR = 1.67; 95% CI, 0.32 to 10.70), in whom tumors were more commonly receptor-negative. The Royal Marsden trial analyzed the entire coding regions of *BRCA1* and *BRCA2* genes in 62 of the 70 women with diagnosed breast cancer. Only four cases with *BRCA1/2* mutations were identified, a number insufficient to determine the efficacy of tamoxifen by *BRCA* status. The current limited evidence precludes reliable assessment of tamoxifen effects in this setting, and this important issue is unlikely to be resolved by further analyses of completed trials. To date, there are no data on the preventive effect of raloxifene and aromatase inhibitors specifically in *BRCA* mutation carriers.

Testing for CYP2D6 *Allelic Variants in the Prevention Setting*

The cytochrome P450 2D6 gene (*CYP2D6*) encodes the enzyme responsible for catalyzing the conversion of tamoxifen to endoxifen, an active metabolite of tamoxifen.[69] Functional allelic variants (*4 most common in whites and *10 most common in Asians), have been identified in approximately 7% of the population. Lower levels of endoxifen have been observed in women taking tamoxifen who are heterozygous and homozygotes for variant alleles in *CYP2D6* in a dose-dependent manner, or in women treated with concomitant medications that block *CYP2D6*, including certain selective serotonin reuptake inhibitors such as paroxetine.[70] Further, in a small nested case-control study of women who took part in the Italian prevention trial, a higher prevalence of the *CYP2D6* *4/*4 phenotype was observed among women with breast cancer who took tamoxifen compared with controls.[71] Confirmation of these results in larger studies is needed. Given the limited evidence, *CYP2D6* testing is currently not recommended in the preventive setting.

SPECIAL COMMENTARY ON RISK ASSESSMENT AND RISK COMMUNICATION IN THE CONTEXT OF BREAST CANCER RISK REDUCTION

Risk Assessment

Risk assessment is carried out to identify women who are at increased risk of breast cancer and who are more likely to benefit from risk reduction options, including chemoprevention strategies such as taking tamoxifen or raloxifene. Table 2 outlines the different eligibility criteria used in each of the prevention trials to identify women who may benefit from chemoprevention. The greater an individual's risk of developing breast cancer, or the lower the risk of incurring side effects from chemoprophylaxis, the more favorable the risk/benefit ratio from chemoprevention is likely to be. There is no single threshold for separating women at high risk of breast cancer from those who are at low risk. However, a projected 5-year risk of $\geq$ 1.66% using the Gail model is often used as a minimum risk for identifying women for whom chemoprevention is considered appropriate.

There are several mathematical models that estimate the risk of developing breast cancer that may be used in the clinical setting. These risk models are generally based on various combinations of family history, age, reproductive history, race/ethnicity, hormonal factors, and benign breast disease. The models include the Breast Cancer Risk Assessment Model of the NCI, based on the Gail model (available at http://dceg.cancer.gov/tools/riskassessment).[23,72-74] Each risk model is intended for use within a specific target population. A comparison of the performance of some of these models for patients attending a family history clinic has been published by Amir et al.[75] These models have not been validated in all populations.

Risk estimates should be calculated periodically, because a woman's risk of breast cancer increases throughout her lifetime. The Breast Cancer Risk Assessment Tool of the NCI is the most commonly used model in the United States to assess a woman's risk of developing invasive breast cancer. It has been validated for use in most women age 35 years or older and provides an individual's 5-year and lifetime risk estimates for developing breast cancer (including both receptor-positive and receptor-negative breast cancers) on the basis of five to six questions. Another model, based on the Women's Health Initiative, predicts the risk of ER-positive invasive breast cancers in postmenopausal women, a target subgroup for prevention with both tamoxifen and raloxifene treatment, and includes only three variables: age, prior breast biopsy, and first-degree relatives with breast cancer.[76]

In women with a strong family history of breast cancer (ie, families with two or more first- or second-degree relatives from the same side of the family, one or more first- or second-degree relatives younger than age 50 years diagnosed with breast cancer), the Claus[72] or the Tyrer-Cuzick[74] models, which incorporate detailed family history, are often used. These high-risk women are generally referred to special clinics for cancer risk education, counseling, genetic testing, and breast cancer risk reduction recommendations. Information about individuals in whom genetic susceptibility testing and evaluation for *BRCA1* and *BRCA2*, Li-Fraumeni's, and Cowden's Syndrome should be considered and can be found in the ASCO Genetics Report,[77] as well as in the National Comprehensive Cancer Network clinical practice guideline for genetic/familial high-risk assessment (available at http://www.nccn.org/professionals/ physician_gls/PDF/genetics_screening.pdf).

The Women's Contraceptive and Reproductive Experiences (CARE) model provides more sensitive estimates for African American women.[73] Gail et al[73] suggest the use of this model for counseling African American women regarding their risk of breast cancer. Unlike the Breast Cancer Risk Assessment Tool, the CARE model has not been used in risk reduction trials. Both the Breast Cancer Risk Assessment Tool and the CARE model are available from the NCI's Web site (http://dceg.cancer.gov/tools/riskassessment).

Although risk models that were developed to predict at the population level are increasingly used to predict events at the individual level, clinicians have been slow to use risk assessment tools in practice.[78-80] However, the increasing use of electronic health records enables easy access to clinical data and online use of models and might improve this situation in the future.

There are important uncertainties associated with patient-level risk assessment.[81,82] Risk models that do well in predicting the proportion of women in a population who develop cancer ("calibration") had only modest ability to discriminate whether an individual woman would or would not develop breast cancer ("discriminatory accuracy").[83] When using such risk models in clinical practice, it is important to disclose that most women identified as being at increased risk for breast cancer will never develop breast cancer, and most women who develop breast cancer are not in an identified increased risk category.

The best that can be done is to present women with an estimate of their future risk, the expected benefits and risks of their risk reduction options, and the inherent uncertainties associated with individual prediction.

Risk Communication

If a woman is identified to be at elevated risk for breast cancer, an informed discussion of risk reduction strategies, including disclosure of risks and benefits, should be initiated while being sensitive to her personal needs and values—including race, culture, and socioeconomic status. Specifically, the potential impact of each agent on the incidence of both noninvasive and invasive breast cancers should be addressed, because the efficacy of different agents varies for these end points, and the biologic potential of these two types of tumors differs. This discussion should include information on ER-positive and ER-negative breast cancers.

Health care professionals should keep in mind that the manner in which risk information is presented, worded, and framed can affect how it is interpreted.[84-90] Risks can be communicated verbally, numerically, or visually. Visual displays can aid both comprehension and understanding of risk perceptions, although information about use of graphics in risk communication is quite preliminary.[91-95] Table 11 provides suggestions regarding risk communication. The suggestions derive from a limited number of studies, as well as consensus reports or systematic reviews.[81,85,101,102,110-115] Additional information about risk communication is available from the following Web sites: (1) http://outcomes.cancer.gov/areas/pcc/communication/, (2) http://decisionaid.ohri.ca/index.html, (3) http://ipdas.ohri.ca/, (4) http://dccps.nci.nih.gov/DECC/riskcommbib/, and (5) http://www.nccn.org/. It is recommended that health care providers present women with the risks and benefits in both absolute and relative terms,[90] which will help to avoid emphasizing the benefits or harms of treatment approaches.

Interpreting Relative and Absolute Risks

Relative risks and absolute risks provide different types of information regarding the magnitude of the effect of an intervention or risk factor. Relative risks are often used in scientific articles because they tend to be independent of baseline risk factors and can most simply summarize the proportion of disease that is related to the particular intervention or risk factor. However, when assessing the public health impact of an intervention or factor, it can be misleading for exactly this reason. Reducing a risk from 2 in a million to 1 in a million, for example, or from 20% to 10%, both lead to a relative risk of 0.50, but, of course, the latter has a much larger public health and personal health impact. Absolute risks capture this aspect of effect size, but suffer from the fact that they relate to the baseline risk associated with the factor under consideration and, of particular relevance to chemopreventive interventions, the duration of the effect. A woman at a baseline risk of 12/1,000 per year would stand to gain twice the absolute benefit of a woman with a risk of 6/1,000 per year, and if the side effect profiles are similar for these two women, the benefit-risk ratio would be twice as large in the former case. Further, for an individual with a baseline risk of breast cancer of 6/1000 per year, an intervention that has a relative risk of 0.50, for example, would reduce the absolute risk in a person by 1.5% over the first 5 years of follow-up. However, if that same relative risk was sustained for 10 years (as may be the case for 5 years use of tamoxifen), the reduction in absolute risk would be twice as large (3%). The NNTs also are affected, being one in 66 in the first case, but one in 33 for a longer duration of protection. Thus relative risks can provide a simple scientific measure of the effect size, but they need to be converted into absolute risks for an individual, and this

Table 11. Approaches to Consider When Communicating Risk

Approach	Rationale
Provide clear and concise information	This will help to avoid information overload and ensure that recipients do not need to make inferences or perform calculations.[96]
Highlight the most important information	Comprehension is better when the presentation format makes the most important information easier to evaluate and when less cognitive effort is required.
Use a constant denominator	The denominator of risk fractions should be kept constant to reduce cognitive effort and increase comprehension (eg, 5 of 100 compared with 15 of 100; not 1 of 50 compared with 1 of 1,000).[97-99] Smaller denominators of 10 or 100 are understood more easily than larger denominators.[100]
Use consistent numeric formats	This will help to facilitate interpretation and comprehension (eg, avoid mixing percentages with odds or frequencies).[101]
Round to whole numbers	Data that are rounded off and presented as whole numbers are understood more easily than numbers with decimals.[101]
Present both absolute and relative risk information	When possible, both the risks and benefits of any intervention should be presented using both absolute and relative risk terms.[102,103]
	Framing the benefits of treatment in relative rather than absolute terms can bias a patient's perception of a therapy's effectiveness,[104] making the benefits of a treatment appear more favorable,[105] or conversely, emphasizing its risks (ie, losses).[106]
Explain significance of risk threshold	It is useful to provide a way for the patient to interpret a given numeric risk value, in terms of whether it is above or below a threshold that reflects higher risk. Risk management recommendations should then be matched to risk level.
Present risks over the most relevant time span	Information is more meaningful when presented with the relevant time span over which events might occur. When comparing risks, the same time span should be used.[97,107]
Be cautious when using descriptive words	Descriptive words (eg, "highly uncertain") are useful and widely understood; however, they should be used with caution, because interpretation of such terms has been shown to be highly variable.[87,108,109]
Use visual aids	*Charts and graphs:* Bar charts are preferred for making comparisons, while line graphs are preferred for showing trends over time or interactions.
	Presentation format: It may be helpful to have more than one presentation format, and allow patients to choose what they prefer.
	Explanations: Clear, concise, yet comprehensive explanations should be provided of what each graph means and specific conclusions.

requires integrating other factors into the equation, such as annual baseline risk and the duration of the effect of the intervention.

HEALTH DISPARITIES

Access to Health Care

Because this clinical practice guideline represents expert recommendations on the best practices in breast cancer risk reduction, it is important to note that many women have limited access to medical care. Racial and ethnic disparities are often a reflection of limited access to health care in the United States. Patients with cancer who are from racial/ethnic minority groups also suffer disproportionately from comorbidities, they experience more substantial obstacles to receiving care, are more likely to be uninsured or underinsured, and are at greater risk of receiving care of poor quality compared with other Americans.[116-118] Women are more likely to seek preventive measures if they are not from a racial/ethnic minority group and if they are insured.[79,119] Evidence from the STAR trial, for example, suggests that white women were more than three times as likely as African American and Hispanic women, and insured women were twice as likely as uninsured women, to have had a breast biopsy.[119]

Furthermore, many patients at increased risk of breast cancer lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of care to these vulnerable populations.

Participation in Clinical Trials

Women from racial/ethnic minority groups are underrepresented in breast cancer prevention trials.[120] Although the STAR trial attempted to increase recruitment of minority women, only 6.5% of participants were women from racial/ethnic minority groups.[4] This participation rate was double that of the initial NSABP-P1 trial. Risk assessment models specific to women from different races/ethnicities may increase the number of potentially eligible women for risk reduction clinical trials.[73] In addition, increased educational and targeted recruitment efforts of women from minority groups into clinical trials is one mechanism through which health disparities can be better understood and ultimately may assist in decreasing disparities in health outcomes.[121,122]

Identification of Women Eligible for Breast Cancer Risk Reduction

To ensure that all women who are at risk of breast cancer are identified, efforts should be made to validate existing breast cancer risk assessment models for women from different races/ethnicities and to develop new population-specific models when appropriate.[123] The introduction of the CARE model offers, in general, a more valid estimate of projected breast cancer risk among African American women. The CARE model is recommended for use among African American women to assess their risk of breast cancer. To use this model, refer to tables published by Gail et al (http://www.cancer.gov/bcrisktool/).[124]

Information about breast cancer risk, prevention, and participation in clinical trials should be developed and tailored in ways that are

culturally relevant and sensitive to the needs of women from a range of racial, ethnic, cultural, and socioeconomic backgrounds. Such efforts will help to eliminate the disparities observed in women seeking breast cancer risk reduction information and interventions and may increase the clinical trial participation of women from minority groups.[120,125]

FUTURE DIRECTIONS

Ongoing randomized clinical trials are being conducted to identify whether aromatase inhibitors will further reduce the incidence of ER-positive invasive breast cancer. In addition, in a randomized clinical trial among women age 60 to 85 years with osteoporosis, tibolone, a synthetic steroid, was associated with a significant reduction in breast cancer incidence similar to tamoxifen and raloxifene and a reduction in colon cancer and fractures, but an increase in stroke compared with placebo, leading to the trial being stopped after 3 years.[126] Further understanding of the effects of tibolone on the breast will assist in understanding its potential as a risk reduction agent. A reduction in breast cancer risk was also observed in another randomized trial that evaluated 5 years of lasofoxifene, a novel SERM compared with placebo in postmenopausal women with osteoporosis. Vertebral fractures were also reduced, whereas VTEs and endometrial cancer were increased.[127] Preventive agents for ER-negative breast cancers (eg, retinoids) are also needed and are being evaluated in early-phase trials.

To ensure that women at risk of breast cancer are given the option of taking preventive agents in an informed manner, breast cancer risk assessment and risk communication need to become an integral part of clinical practice. A broader educational effort is needed to alert women from all racial/ethnic and socioeconomic groups, as well as primary care providers, that treatment is available to reduce breast cancer risk. For example, integration of risk reduction information and intervention would fit naturally into breast screening clinics, as women who attend these clinics are already sensitized to the need to take preventive action. Clinical tools and resources that can assist this educational effort are available at www.asco.org/guidelines/bcrr. More consistent reporting of outcomes and adverse effects in future prevention trials will also assist in results being more easily summarized and compared, when appropriate, for translation into clinical practice, such as in these practice guidelines. Lastly, new approaches are needed to inform African American women, and other nonwhite minorities, of the potential value of participating in breast cancer prevention trials.

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